

Novartis Institutes for BioMedical Research

VAY736

Clinical Trial Protocol CVAY736X2201

A single dose, double-blind, placebo-controlled, parallel study to assess the pharmacodynamics, pharmacokinetics and safety and tolerability of VAY736 in patients with primary Sjögren's syndrome

Personal Data

Document type:	Amended Protocol Version
EUDRACT number:	2013-000250-22
Version number:	v06 Clean (incorporating Amendment 06)
Study phase:	Ila
Document status:	Final
Release date:	31-Oct-2016

Property of Novartis
Confidential
May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Notification of serious adverse events

A serious adverse event (SAE) is any event which is fatal or life-threatening, which requires or prolongs hospitalization, which is significantly or permanently disabling or incapacitating, which constitutes a congenital anomaly or a birth defect, or which is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any SAE occurring in a subject **from consent until 30 days after stopping the trial/study drug** must be reported either on the paper SAE report form or via the electronic SAE form within the clinical data capture system (where available).

For SAEs reported using the **paper SAE report form**, the investigator will ensure that the form is completed and **faxed** by the **investigator to the local Novartis Drug Safety and Epidemiology Department within 24 hours** of learning of the occurrence of the SAE even if the SAE does not appear to be drug-related. The original SAE form, together with the fax confirmation sheet, must be kept with the case report forms at the study site.

For SAEs recorded *electronically* in the Novartis clinical data capture system, information should be **entered, saved and e-signed within 24 hours of awareness of the SAE**. These data will automatically be submitted to Novartis Drug Safety and Epidemiology.

More details in **Section 7** of this protocol.

Corporate Confidential Information

Any update to the Novartis DS&E or personnel information required during the course of the study will be communicated directly to the relevant Investigator site(s); a specific protocol amendment should not be required.

Table of contents

Notification of serious adverse events.....	2
Table of contents	3
List of tables	7
List of figures	7
List of abbreviations	8
Pharmacokinetic definitions and symbols	11
Glossary of terms	12
Corporate Confidential Information	
Protocol synopsis.....	32
Assessment schedule	36
1 Introduction	41
1.1 Background	41
Corporate Confidential Information	
1.2 Study purpose	48
2 Study objectives.....	49
2.1 Primary objectives	49
2.2 Secondary objectives	49
2.3 Exploratory objectives	49
3 Investigational plan	50
3.1 Study design.....	50
3.1.1 Dose escalation decision	52
3.2 Rationale of study design.....	53
3.3 Maintenance of subject/study site personnel blinding.....	54
3.4 Rationale of dose/regimen, duration of treatment	55
3.5 Rationale for choice of comparator	56
3.6 Purpose and timing of interim analyses/design adaptations	56
3.7 Risks and benefits	56
3.7.1 Potential risks associated with exposure to VAY736	57
3.7.2 Risk of ultrasound contrast agent	59
3.7.3 Pre-medication	59

	3.7.4	Risk mitigation strategy	60
4		Population.....	60
	4.1	Inclusion criteria	61
	4.2	Exclusion criteria	61
5		Treatment.....	64
	5.1	Protocol requested treatment	64
	5.1.1	Investigational treatment.....	64
	5.1.2	Additional study treatment.....	65
	5.2	Treatment arms	65
	5.3	Treatment assignment.....	66
	5.4	Treatment blinding.....	66
	5.5	Treating the subject.....	67
	5.5.1	Subject numbering	67
	5.5.2	Dispensing the study treatment	68
	5.5.3	Handling of study treatment.....	68
	5.5.4	Instructions for prescribing and taking study treatment.....	69
	5.5.5	Permitted dose adjustments and interruptions of study treatment	69
	5.5.6	Recommended treatment of adverse events	69
	5.5.7	Rescue medication	70
	5.5.8	Concomitant treatment	70
	5.5.9	Prohibited treatment	71
	5.5.10	Discontinuation of study treatment and premature subject withdrawal.....	71
	5.5.11	Emergency unblinding of treatment assignment.....	74
	5.5.12	Study completion and post-study treatment.....	74
	5.5.13	Early study termination	74
6		Visit assessments.....	75
	6.1	Dietary, fluid and other restrictions	75
	6.2	Subject demographics/other baseline characteristics.....	76
	6.3	Treatment exposure and compliance	76
	6.4	Efficacy / Pharmacodynamic assessments.....	77
	6.4.1	ESSDAI.....	77
	6.4.2	ESSPRI.....	77
	6.4.3	SF-36	77
	6.4.4	MFI.....	77

Corporate Confidential Information

6.4.8	Assessment of salivary flow	79
Corporate Confidential Information		
6.5	Safety	81
6.5.1	Physical examination	81
6.5.2	Vital signs.....	81
6.5.3	Height and weight	81
6.5.4	Laboratory evaluations	81
6.5.5	Electrocardiogram (ECG)	83
6.5.6	Pregnancy	83
6.5.7	Other safety assessments	84
6.6	Pharmacokinetic assessments	84
Corporate Confidential Information		
6.6.3	Pharmacokinetic parameters	85
Corporate Confidential Information		
6.8	Other assessments.....	86
Corporate Confidential Information		
7	Safety monitoring	89
7.1	Adverse events.....	89
7.2	Serious adverse event reporting.....	90
7.3	Liver safety monitoring	92
7.4	Pregnancy reporting.....	92
7.5	Early phase safety monitoring	93
8	Data review and database management.....	93
8.1	Site monitoring	93
8.2	Data collection	93
8.3	Database management and quality control	94
8.4	Data Monitoring Committee.....	95
8.5	Adjudication Committee.....	95
9	Data analysis.....	95
9.1	Analysis sets	95

	9.2	Subject demographics and other baseline characteristics	95
	9.3	Treatments (study drug, rescue medication, other concomitant therapies, compliance).....	95
	9.4	Analysis of the primary variable.....	96
	9.4.1	Variable(s).....	96
	9.4.2	Statistical model, hypothesis, and method of analysis	96
	9.4.3	Handling of missing values/censoring/discontinuations	97
	9.5	Analysis of secondary and exploratory variables	97
	9.5.1	Efficacy / Pharmacodynamics	97
	9.5.2	Safety.....	98
	9.5.3	Pharmacokinetics	99
	9.5.4	Pharmacokinetic / pharmacodynamic interactions.....	99
		Corporate Confidential Information	
	9.5.7	Other biomarkers.....	100
	9.6	Sample size calculation.....	100
C	9.7	Power for analysis of key secondary variables	101
		Corporate Confidential Information	
10		Ethical considerations.....	102
	10.1	Regulatory and ethical compliance.....	102
	10.2	Informed consent procedures.....	102
	10.3	Responsibilities of the investigator and IRB/IEC.....	103
	10.4	Publication of study results.....	103
11		Protocol adherence	103
	11.1	Protocol Amendments	103
12		References	104
		Corporate Confidential Information	
15		Appendix 3: ESSDAI	111
16		Appendix 4: ESSPRI	115
17		Appendix 5: SF-36	119
18		Appendix 6: MFI.....	120
		Corporate Confidential Information	

List of tables

Table 1-1	Summary (geometric mean) of PK parameters of VAY736 in RA patients following a single i.v. dose of 0.0003 mg/kg to 10.0 mg/kg (CVAY736X2101).....	47
Table 5-1	Study drug VAY736	64
Table 5-2	Prohibited treatment	71
Table 14-1	Liver Event Definitions.....	108
Table 14-2	Liver Event Follow Up Requirements	109
Table 15-1	The EULAR Sjögren's syndrome disease activity index (ESSDAI): domain and item definitions and weights.....	111
Table 20-1	Blinding levels	122

Corporate Confidential Information

Figure 3-1	Study design	53
Figure 9-1	Probability of meeting efficacy criteria for N=16:8 VAY736:placebo.....	101

List of abbreviations

ADA	Anti Drug Antibody
ADCC	Antibody-dependent cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANA	Anti-nuclear antibody
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BAFF	B cell activating factor
BAFF-R	BAFF-Receptor
b.i.d.	Twice a day
BM	Biomarker
BMI	Body Mass Index
BUN	Blood urea nitrogen
CD-ROM	Compact disc – read only memory
CFR	Code of Federal Regulation
CK	Creatinine kinase
CLL	Chronic lymphocytic leukemia
CRF	Case Report/Record Form (paper or electronic)
CRP	C-reactive protein
CO2	Carbon dioxide
CRO	Contract Research Organization
CV	Coefficient of variation
DLT	Dose limiting toxicity
DMARDS	Disease-modifying anti-rheumatic drugs
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay

EOS	End Of Study
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Response Index
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FIH	First in human
GCP	Good Clinical Practice
γ-GT	Gamma-glutamyl transferase
h	Hour
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
i.v.	intravenous
IVIG	Intravenous Immunoglobulin
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LLN	Lower limit of normal
mAb	Monoclonal antibody
MFI	Multidimensional Fatigue Inventory
mg	Milligram(s)
ml	Milliliter(s)
NCA	Non compartmental analysis
NG sequencing	Next generation sequencing
NK	Natural killer cells
NR	Not reported
o.d.	Once a day
OSS	Ocular staining score
PA	Posteroanterior

PD	Pharmacodynamic(s)
PEE	Punctate epithelial erosions
PK	Pharmacokinetic(s)
p.o.	Oral
PPD	Purified protein derivative
pSS	Primary Sjögren's Syndrome
RA	Rheumatoid arthritis
RBC	Red blood cell(s)
REB	Research Ethics Board
RF	Rheumatoid factor
SAE	Serious adverse event
SCA	Salivary collection aid
SF-36	Short Form (36) Health Survey
SLE	Systemic lupus erythematosus
s.c.	Subcutaneous
SAD	Single ascending dose
SD	Single dose
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SD	Standard deviation
sm/sl	submandibular/sublingual
TBL	Total bilirubin
TBUT	Tear breakup time
TK	Toxicokinetics
TMDD	Target Mediated Drug Disposition
ULN	Upper limit of normal
ULQ	Upper limit of quantification
VAS	Visual analog scale
WBC	White blood cell(s)

Pharmacokinetic definitions and symbols

AUC _{0-t}	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUC _{inf}	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUC _{last}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
C _{max}	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
T _{1/2}	The terminal elimination half-life [time]
T _{max}	The time to reach the maximum concentration after drug administration [time]
V _z	The volume of distribution during the terminal elimination phase following intravenous administration [volume]
V _{ss}	The volume of distribution at steady state following intravenous administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	<p>All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls.</p> <p>This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination.</p> <p>Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.</p>
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.

Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Protocol synopsis

Protocol number	CVAY736X2201
Title	A single dose, double-blind, placebo-controlled, parallel study to assess the pharmacodynamics, pharmacokinetics and safety and tolerability of VAY736 in patients with primary Sjögren's syndrome
Brief title	VAY736 in patients with primary Sjögren's syndrome
Sponsor and Clinical Phase	Novartis Pharma AG Phase IIa
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study with VAY736 monoclonal antibody is designed to evaluate the safety, tolerability, PD and PK, and to explore therapeutic efficacy of a single intravenous infusion of VAY736 monoclonal antibody in pSS patients to enable further development of the compound for treatment of this disease population.
Primary Objectives and Key Secondary Objective	<ul style="list-style-type: none"> To compare the effect of a single i.v. dose VAY736 versus placebo on the clinical disease activity of primary Sjögren's syndrome patients as measured by the change of a modified EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) between base line and week 12 To assess the safety and tolerability of a single i.v. dose VAY736 in patients with primary Sjögren's syndrome as measured by adverse events (AEs)
Secondary Objectives	<ul style="list-style-type: none"> To evaluate the effect of a single i.v. dose VAY736 versus placebo on self-reported outcomes in pSS patients at 12 weeks compared to baseline as measured by the EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI), the Short Form (36) Health Survey (SF-36) and the Multidimensional Fatigue Inventory (MFI) Questionnaire. To determine the changes in the physician global assessment of the patient's overall disease activity between baseline and week 12 as recorded by a visual analog scale (VAS) To determine the changes in the patients' global assessment of their disease activity between baseline and week 12 as recorded by a VAS To determine the pharmacokinetics following a single dose i.v. VAY736 in pSS patients
Study design	Randomized, double blind, placebo-controlled, non-confirmatory study in approximately 26 patients. Patients that received placebo treatment will be offered open-label single dose i.v. VAY736 treatment
Population	Seropositive primary Sjögren's syndrome
Inclusion criteria	<ul style="list-style-type: none"> Fulfilled revised European US consensus criteria for pSS ESSDAI value ≥ 6 Elevated serum titers at screening of ANA ($\geq 1:160$) and of RF or <ul style="list-style-type: none"> Seropositive at screening for anti-SSA (\pmanti-SSB) antibodies Stimulated whole salivary flow rate at screening of > 0 mL/min

Exclusion criteria	<p>Corporate Confidential Information</p>
	<ul style="list-style-type: none"> • Prior use of any B-cell depleting therapy (e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb) • Prednisone > 10 mg/d or dose change within 2 weeks of the time of randomization • Any of the following within 180 days of randomization <ul style="list-style-type: none"> • Anti-BAFF mAb • CTLA4-Fc Ig (abatacept) • Anti-TNF-α mAb • Intravenous Ig • Plasmapheresis • i.v. or oral cyclophosphamide • Treatment with azathioprine, or prior use within 84 days of randomization; patients taking either hydroxychloroquine or methotrexate at a consistent dose for ≥ 3 months prior to randomization are eligible if dose is maintained throughout the study <p>Corporate Confidential Information</p> <ul style="list-style-type: none"> • Active viral, bacterial or other infections at the time of screening or enrollment, or history of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms • History or evidence of tuberculosis • Receipt of live/attenuated vaccine within a 2 month period before enrollment <p>Corporate Confidential Information</p> <ul style="list-style-type: none"> • History of primary or secondary immunodeficiency <p>Corporate Confidential Information</p>
Investigational and reference therapy	<ul style="list-style-type: none"> • VAY736 3 mg/kg and 10 mg/kg administered intravenously. • Control: VAY736 placebo infusions will be prepared by an unblinded pharmacist. • Duration of treatment: single i.v. dose administration and a follow up study up to 1 month after a patient's circulating B cells meet criteria for recovery.

Efficacy assessments	<ul style="list-style-type: none"> • PD assessment of circulating B cell levels • Modified EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) • EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI) • Short Form (36) Health Survey (SF-36) • Multidimensional Fatigue Inventory (MFI) Questionnaire • Physician's and Patient's assessment of global disease activity • High resolution ultrasound of salivary glands (with optional blood flow) <p>Corporate Confidential Information</p>
	<ul style="list-style-type: none"> • Salivary gland function using salivary flow (unstimulated and stimulated) <p>Corporate Confidential Information</p>
Safety assessments	<ul style="list-style-type: none"> • Lacrimal gland function using the Ocular staining score (OSS) • Serum evidence of B cell hyperactivity. <p>Corporate Confidential Information</p>
	<ul style="list-style-type: none"> • Physical exam • Vital signs • Laboratory evaluations: hematology, clinical chemistry, urinalysis • Electrocardiogram (ECG) • Pregnancy testing • Occurrences of infection • Adverse event • Serious adverse event • Concomitant medications <p>Corporate Confidential Information</p>
	<ul style="list-style-type: none"> • Flow cytometry safety panels <p>Corporate Confidential Information</p>
Other assessments	<p>Corporate Confidential Information</p>
	<ul style="list-style-type: none"> • Pharmacokinetics <p>Corporate Confidential Information</p>

Data analysis	<p>The primary efficacy variable is the ESSDAI recorded at baseline and week 6, 12 and 24.</p> <p>The change from baseline in ESSDAI will be analyzed using a model including terms for the patient effect (as a random effect), treatment effect, time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with the baseline ESSDAI as a covariate. This statistical analysis model will include change from baseline data on the ESSDAI from all post-baseline time points at which it was recorded (i.e., weeks 6, 12 and 24) but the primary comparison is made for week 12.</p> <p>Estimates of the difference between VAY736 and placebo at each time point will be derived from this model and presented together with 95% credible intervals. A positive sign of therapeutic effects will be considered to be a difference of at least 5 points in the change from baseline between VAY736 and placebo with a moderate level of evidence (i.e., 50%). Additionally there should be a high level of evidence (i.e., 90%) that there is a difference between VAY736 and placebo. The estimates of the posteriors probabilities of these criteria being met will be provided, assuming standard non-information prior Normal distributions.</p> <p>Secondary efficacy variables (ESSPRI, SF-36, MFI) physician global assessment of the patient's overall disease activity, patient's global assessment of their disease activity) will be analyzed following a similar approach. Other assessments supporting the exploratory objectives will be summarized</p>
Key words	Primary Sjögren's syndrome, BAFF-R, B cell depletion

Assessment schedule

Study phase	Scr.	BL	Treatment			Follow-up									Long term Follow-up ¹⁵		End of Study ¹⁶
Visit Numbers	V1	V2	V3		V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 – V16	V18, V20, V24, V25, V26 ...	V777
Day	-35 to -8	-7 to -1 ¹⁷	1		2	7	14	21	42	63	84	112	140	168	224, 280, 364	532, 700, 1036, 1372, 1708 ...	-
Week	-	-	1				2	3	6	9	12	16	20	24	32, 40, 52	76, 100, 148, 196, 244 ...	-
Time (h)	-	-	0	2 ¹³	24	-	-	-	-	-	-	-	-	-	-	-	-
Allowed time window	-	-	-	-	-	±1d	±2d	±2d	±4d	±4d	±4d	±4d	±4d	±4d	±2 weeks	±2 weeks	Within 6wk
Inclusion /Exclusion criteria	x	x															
Relevant medical history / current medical conditions	x	x															
Demography	x																
Physical examination ⁶	x	x			x	x	x		x		x	x	x	x	x		x
Hepatitis and HIV screen	x																
Urine drug and alcohol screen	x	x															
Pregnancy test ⁷	x	x															x
Purified protein derivative (PPD) skin test or QuantiFeron test	X ²⁰																
Vital signs and body measurements ¹	x	x	x<-->x		x	x	x		x		x	x	x	x	x		x
ECG evaluation	x	x			x	x	x		x		x	x	x	x	x		x
Hematology, blood chemistry, urinalysis	x	x			x	x	x		x	x	x	x	x	x	x	x ²⁶	x
Randomization		x															
Drug administration ¹³			X <--> X														
Modified ESSDAI ²	x	x							x		x			x			x ²¹
ESSPRI, SF-36, MFI ³		x							x		x			x			x ²¹

Study phase	Scr.	BL	Treatment			Follow-up									Long term Follow-up ¹⁵		End of Study ¹⁶
Visit Numbers	V1	V2	V3		V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 – V16	V18, V20, V24, V25, V26 ...	V777
Day	-35 to -8	-7 to -1 ¹⁷	1		2	7	14	21	42	63	84	112	140	168	224, 280, 364	532, 700, 1036, 1372, 1708 ...	-
Week	-	-	1				2	3	6	9	12	16	20	24	32, 40, 52	76, 100, 148, 196, 244 ...	-
Time (h)	-	-	0	2 ¹³	24	-	-	-	-	-	-	-	-	-	-	-	-
Allowed time window	-	-	-	-	-	±1d	±2d	±2d	±4d	±4d	±4d	±4d	±4d	±4d	±2 weeks	±2 weeks	Within 6wk
VAS Physician		X							X		X			X	X		X ²¹
Patient Global Assessment		X							X		X			X	X		X
Corporate Confidential Information	X										X						
Corporate Confidential Information	X								X		X			X	X		X ²¹
Flow cytometry panels ⁴			X		X	X	X	X	X	X	X	X	X	X	X ²²	X ²⁵	X ²¹
Corporate Confidential Information			X		X	X	X	X	X	X	X	X	X	X			X ²¹
Corporate Confidential Information		X							X		X			X			
B cell hyperactivity ¹⁰	X								X		X			X		X ²⁷	X ²¹
Corporate Confidential Information		X									X						X
HR Contrast Ultrasound ⁹	X								X		X			X			
Ocular staining score	X								X		X			X			X ²¹
Salivary flow test ⁸	X	X							X		X			X			X ²¹
PK blood collection			X	X ¹⁴	X	X	X	X	X	X	X	X	X	X			X
Corporate Confidential Information			X	As required ²³				X	As requ. ²³		X	As requ. ²³		X	As requ. ²³		X
Corporate Confidential Information		X															
(S)AEs ¹⁹	As required																

Study phase	Scr.	BL	Treatment			Follow-up									Long term Follow-up ¹⁵		End of Study ¹⁶
Visit Numbers	V1	V2	V3		V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 – V16	V18, V20, V24, V25, V26 ...	V777
Day	-35 to -8	-7 to -1 ¹⁷	1		2	7	14	21	42	63	84	112	140	168	224, 280, 364	532, 700, 1036, 1372, 1708 ...	-
Week	-	-	1				2	3	6	9	12	16	20	24	32, 40, 52	76, 100, 148, 196, 244 ...	-
Time (h)	-	-	0	2 ¹³	24	-	-	-	-	-	-	-	-	-	-	-	-
Allowed time window	-	-	-	-	-	±1d	±2d	±2d	±4d	±4d	±4d	±4d	±4d	±4d	±2 weeks	±2 weeks	Within 6wk
Concomitant meds / therapies	As required																
Study completion information																	x
	Amb.	**	Domiciled				Ambulatory										

- C
- ¹ Vital signs: Sitting and standing blood pressure and heart rate measurement required (standing only at screening and baseline); body height (at screening only), body weight, temperature. During study drug administration blood pressure and heart rate should be obtained every 30 minutes.
 - ² ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index ([Section 6.4.1](#)).
 - ³ ESSPRI: EULAR Sjögren's Syndrome Patient Response Index ([Section 6.4.2](#)),
SF-36: Short Form (36) Health Survey ([Section 6.4.3](#)),
MFI: Multidimensional Fatigue Inventory ([Section 6.4.4](#)).
- Corporate Confidential Information
-
- ⁶ At Screening and Baseline perform a thorough physical examination. At the subsequent visits assess relevant organ systems.
 - ⁷ Pregnancy test: Perform on all females: At screening perform a serum pregnancy test; at Baseline and the EOS visit a urine pregnancy test is sufficient.
 - ⁸
Corporate Confidential Information
-
- ¹⁰ B cell hyperactivity: Corporate Confidential Information
Corporate Confidential Information
-
- ¹³ Administration: VAY736 infusion over 2 hours following premedication with paracetamol (500 mg 1 hour pre-dose and 5 hours [±30 min.] post dose and 1000 mg 11 hours [±1 hour] post dose). H1 receptor blockers may be administered in the event paracetamol pre-medication does not prevent infusion reactions sufficiently. The decision may be made on a case-by-case basis or as a general recommendation if the paracetamol pre-medication is deemed not effective during conduct of the study.
 - ¹⁴ To be taken at the end of infusion.
 - ¹⁵ Long term follow-up: only in patients with persisting B cell depletion defined as either of the following listed below:
a) lower limit of normal (50 cells/μL) or, b) 20% from baseline levels. If B cell recovery criteria are not met by week 24 (Day 168) the affected patient should be followed-up. The visits should take place at week 32, 40, 52, week 76 and week 100 [±2 weeks] and thereafter every 48 weeks (week 148, 196 and so forth [±2 weeks]) until the patient no longer meets any of the criteria used to define persisting B cell depletion.
 - ¹⁶ End of Study: Visit 777 will be performed within 4 weeks from the visit B cell depletion is no longer persistent (Visit 13 or during long term follow-up).
 - ¹⁷ Baseline assessments should be completed between Days -7 and -1.
Corporate Confidential Information

- ¹⁹ All adverse events will be reported from the time the subject has provided informed consent to visit 16 (week 52). Starting from visit 17 until end of study, only AE related to VAY736 as assessed by the investigator and AE related to infection, potential malignant events and neutropenia will be recorded. Serious adverse events will be reported from the time the subject has provided informed consent until 30 days after the last study visit. Any SAEs experienced after the 30-day period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.
- ²⁰ PPD / QuantiFeron test: At screening or within 6 months prior to randomization.
- ²¹ Only in patients who do not meet end of study criteria at week 24.
Corporate Confidential Information

** optional overnight stay at Day -1.

1 Introduction

1.1 Background

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease of unknown etiology characterized by lymphoid infiltration and progressive destruction of exocrine glands (Youinou and Pers 2012). Although primarily organ-specific for the lacrimal and salivary glands, the inflammatory process can target any organ. Thus, the clinical features range from dryness, pain and fatigue affecting nearly all patients, to severe, extra-glandular and systemic involvement in a more limited subset. The increased B cell activity underlying pSS also results in an increased risk for malignant transformation, with lymphoma development occurring in 5% of Sjögren's syndrome patients.

Sjögren's syndrome is second only to rheumatoid arthritis (RA) in prevalence as a systemic autoimmune disease. The disease affects mainly women with a female/male ratio of 9:1 and can occur at any age. Treatment for pSS patients is limited to symptomatic care for the mucosal signs and symptoms. Steroids and typical DMARDs are ineffective, and no pharmacologic intervention is effective against the severe, disabling fatigue. Recently, efficacy of B cell depletion therapy using the anti-CD20 monoclonal antibody (mAb) rituximab has been shown for both glandular and extra-glandular manifestations of pSS as well as for lymphoma management.

VAY736 is a human IgG1/κ mAb designed to specifically bind to B cell activating factor receptor (BAFF-R) that is predominantly expressed on B cells, thereby preventing the binding of B cell activating factor (BAFF). BAFF:BAFF-R mediated signaling is critically involved in the maturation of transitional B cells, for survival and activation of mature B cells, and for isotype class switching in response to T cell dependent antigens.

Corporate Confidential Information

Corporate Confidential Information

1.1.1.3 Human safety and tolerability data

As of 15-Jun-2013, human clinical experience with VAY736 is primarily limited to RA patients (n = 41, 31 treated) of mild-to-moderate disease severity in an ongoing phase I study CVAY736X2101 designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics in single- and multiple-ascending doses of the compound.

Corporate Confidential Information

1.2 Study purpose

This study with VAY736 monoclonal antibody is designed to evaluate the safety, tolerability, pharmacokinetics and therapeutic efficacy of a single intravenous infusion of VAY7346 monoclonal antibody in pSS patients to enable further development of the compound for treatment of this disease population.

2 Study objectives

2.1 Primary objectives

- To compare the effect of a single i.v. dose VAY736 versus placebo on the clinical disease activity of primary Sjögren's syndrome patients as measured by the change of a modified EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) between baseline and week 12
- To assess the safety and tolerability of a single i.v. dose VAY736 in patients with primary Sjögren's syndrome as measured by adverse events (AEs)

2.2 Secondary objectives

- To evaluate the effect of a single i.v. dose VAY736 versus placebo on self-reported outcomes in pSS patients at 12 weeks compared to baseline as measured by the EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI), the Short Form (36) Health Survey (SF-36) and the Multidimensional Fatigue Inventory (MFI) Questionnaire.
- To determine the changes in the physician global assessment of the patient's overall disease activity between baseline and week 12 as recorded by a visual analog scale (VAS)
- To determine the changes in the patients global assessment of their disease activity between baseline and week 12 as recorded by a VAS
- To determine the pharmacokinetics following a single dose i.v. VAY736 in pSS patients

2.3 Exploratory objectives

Corporate Confidential Information

- High resolution ultrasound of salivary glands as measured by the following parameters:
 - Salivary gland thickness and staging
 - Parotid salivary gland blood flow with contrast agent (optional)

Corporate Confidential Information

Corporate Confidential Information

- Salivary gland function using the salivary flow (unstimulated and stimulated)
Corporate Confidential Information
 - Lacrimal gland function using the Ocular Staining Score
 - Serum evidence of B cell hyperactivity,
-
- To measure the effect of a single i.v. dose VAY736 on leukocyte subsets,
Corporate Confidential Information

3 Investigational plan

3.1 Study design

This is a double-blind, randomized, placebo-controlled, parallel-group, non-confirmatory study to assess the safety, tolerability, pharmacokinetics, immunogenicity, pharmacodynamics and clinical efficacy of VAY736 administered intravenously as a single dose in pSS patients.

The patients will be enrolled in 2 sequential cohorts:

- 3 mg/kg cohort (Cohort 1): 6 patients randomized to receive a single dose of VAY736 at a starting dose of 3.0 mg/kg or placebo at a 2:1 ratio; approximately 4 patients in this cohort will receive a 3.0 mg/kg dose of VAY736 and approximately 2 patients will receive placebo.
- 10 mg/kg cohort (Cohort 2): 20 patients randomized to receive a single dose of VAY736 at a dose of 10.0 mg/kg or 3.0 mg/kg or placebo at a 6:1:3 ratio, respectively. Around 12 patients will receive 10 mg/kg of VAY736 in this cohort and around 6 will receive placebo. Approximately 2 patients will receive 3.0 mg/kg in this cohort to maintain a level of blinding regarding the dose received.

Between Cohort 1 and Cohort 2 recruitment will be paused and a safety review will be conducted by the VAY736 project team and the principle investigators (see [Section 3.1.1](#)).

Corporate Confidential Information

t This study will enroll around 26 patients with primary Sjögren's syndrome. At least 24 subjects are expected to complete the study.

Subjects that are prematurely withdrawn from the study for reasons other than safety will be replaced on a case by case basis. Data from the withdrawn patients will still be used in the primary analysis as much as possible but the sponsor will use replacement patients to obtain complete data on at least 24 patients.

For each patient, there will be a maximum 28-day screening period. Subjects who meet the eligibility criteria at screening will undergo baseline evaluations (between Days -7 to -1). Patients may stay overnight at the study site on Day -1 if required for scheduled early morning study-related activities on Day 1, but this is not mandatory. All baseline safety evaluation results must be available prior to dosing and meet eligibility criteria.

Enrolled patients will be randomized at a 2:1 ratio to receive treatment with either VAY736 3 mg/kg or placebo in the first cohort. In the second cohort, they will be randomized to receive VAY736 10 mg/kg, 3 mg/kg or placebo at a 6:1:3 ratio. Dosing of the patients in the first cohort and the first 5 patients enrolled in the second cohort will be staggered at a minimum interval of 20 hours. On Day 1, following premedication with paracetamol (and H1 receptor blocker, if necessary), a single dose of VAY736 or placebo will be administered, followed by PK, pharmacodynamics (PD) and safety assessments for up to 24 hours. Patients are required to stay overnight at the study site on Day 1 and will be discharged on Day 2 after completion of all safety assessments and collection of the 24 h blood samples provided there are no safety concerns.

Patients will return to the study center for safety and PK checks at Day 7, Day 14, week 3, week 6, week 9 and week 12. Subsequent outpatient visits will occur at 4 week intervals thereafter until week 24.

At Week 24 the blind will be broken to confirm treatment allocation. Investigators will follow the guidance below:

- If a patient received VAY736 and their B cell recovery) is demonstrated at Week 24 (refer to [Section 6.4.6](#) for B cell recovery definition), then patients should return for their End of Study visit approximately 4 weeks later.
- Those patients who do not meet the criteria for B cell recovery at Week 24, will return to the site every 8 weeks until Week 40, then at week 52, every 24 weeks until 2 years post dose (week 100) and afterwards every 48 weeks, until B cell recovery is demonstrated (refer to [Section 6.4.6](#) for B cell recovery definition) and the End of Study visit may be scheduled.
- If a patient received placebo, they will be offered the option of receiving open-label VAY736 (10 mg/kg) in a separate treatment arm.
 - Patients that consent to open-label VAY736 treatment will restart the study at Day 1 (within 4 weeks [+ 2 week window] of Week 24 visit)
 - Patients that do not consent to receive open-label VAY736 treatment will return to the site for End of Study visit as per [Assessment schedule](#).

Patients will not be informed of their treatment allocation until after all of the assessments scheduled for Week 24 have been completed.

Once B cell recovery threshold criteria are met the patient will undergo the end of study visit within 4 weeks. End of study visit will include study completion evaluations followed by discharge from the study.

Safety assessments at study visits will include vital signs, physical examinations, ECGs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis, pregnancy test), adverse events and serious adverse events monitoring. In particular, subjects will be monitored closely during the first 2 hours after starting infusion of VAY736 for signs or symptoms of adverse events, including development of an infusion reaction. Treatment of infusion reactions is described under [Section 5.5.6](#).

In addition, serum anti-VAY736 antibody levels Corporate Confidential Information ([Section 6.7](#)) will be measured.

For this study of VAY736 in Sjögren's syndrome patients, 4 different flow cytometry-based panels ([Section 6.8.2.1](#)) will be conducted on whole blood to monitor responses of circulating leukocytes to VAY736 exposure and will include a Leukocyte Immunophenotyping Panel,

Additional planned biomarkers of PD effects by VAY736 will include
Corporate Confidential Information

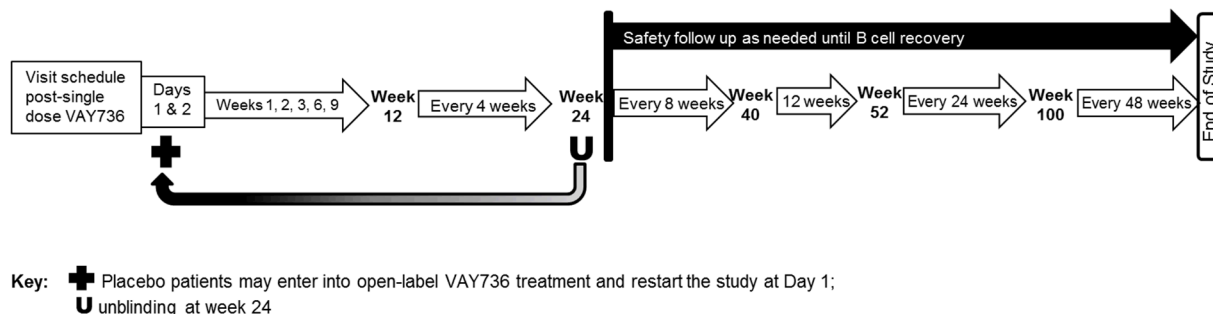
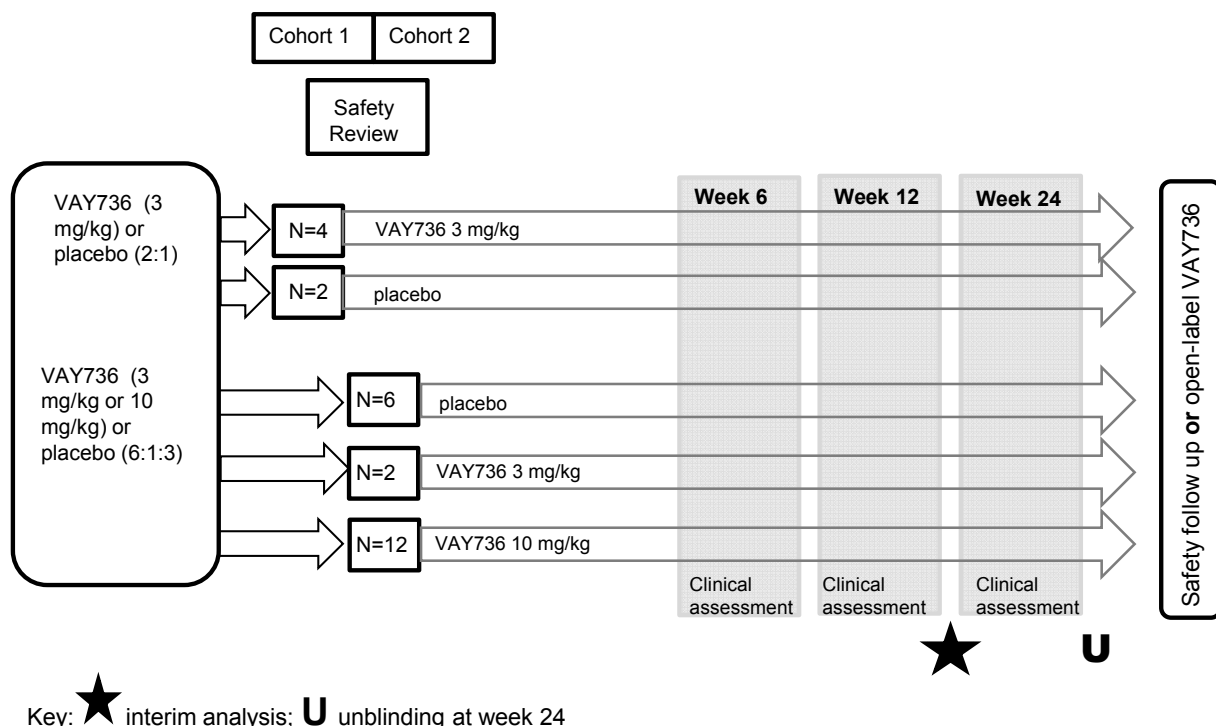
functional evaluations of

lacrimal and salivary glands, measures of B cell hyperactivity and tissue imaging of salivary glands (non-invasive and invasive).

3.1.1 Dose escalation decision

Progression from the 3 mg/kg dose cohort to the 10 mg/kg cohort will require a minimum post-treatment safety observation period of 14 days for all individuals in the prior cohort. This 14-day safety period allows sufficient time for maximum PD effects from VAY736 to develop. The sponsor and the principal investigator will review 14-day safety data a minimum of 14 days after the last subject of this first patient group has received his or her dose of VAY736 at 3 mg/kg to ensure that escalation to the 10 mg/kg dose is appropriate and acceptable. Data available at safety review will be: AEs, SAEs, out-of-range clinical laboratory values, all hematology parameters and flow cytometry safety panels.

Figure 3-1 Study design



An interim analysis is planned after all patients have completed the week 12 visit in order to assess the effect of VAY736 on the primary endpoint.

3.2 Rationale of study design

This study will be conducted in patients with active pSS for which no existing treatment has been proven effective against the underlying disease. Current evidence supports a key role for B cells in pSS pathogenesis and implicates BAFF:BAFF-R signaling as a contributing factor. In addition, B cell targeted therapy with rituximab (anti-CD20 mAb) has demonstrated evidence in pSS patients supporting therapeutic efficacy while maintaining a favorable safety profile in clinical studies to date.

A randomized, placebo-controlled, double-blind approach is used to eliminate potential bias in reporting safety and clinical efficacy data in this first, exploratory study in pSS patients. Patients will be randomized to VAY736 or placebo in an overall 18:8 ratio in order to

minimize exposure to placebo and to gather more data on VAY736
Corporate Confidential Information

Based on published results with a single cycle of rituximab, significant clinical responses in pSS patients can be detected as early as 5 weeks, with maximum effect shown at 12 weeks (Meijer et al 2010). A follow up evaluation at 24 weeks will provide information on the duration of clinical response to VAY736 treatment. Heterogeneity in duration of B cell depletion is expected within a given patient treatment group from experience reported with rituximab Corporate Confidential Information. Therefore, after completion of the 24 weeks evaluation, patients not meeting criteria for B cell recovery will continue under periodic monitoring until such criteria are reached.

3.3 Maintenance of subject/study site personnel blinding

Only the study site pharmacists and the bioanalyst will be unblinded throughout the duration of the study. The bioanalyst will not provide individual PK values until an IA or the end of the study.

The study will be blinded to patients, investigator site staff and the clinical trial team at the time of randomization. Unblinding of patients' treatment allocation, as they reach the end of double-blind treatment period (Week 24), is planned.
Corporate Confidential Information

In order to reduce patient discomfort and help reduce the risk of unblinding that might arise if an infusion reaction occurs, all patients will receive treatment with paracetamol (and histamine H1 receptor blocker, if necessary) prior to infusion with VAY736.

Because of the expected cell depleting effects of VAY736 affecting the patients' leukocyte counts and differentials, an independent safety physician as well as a medical monitor at Novartis will be designated to monitor these safety parameters, for all patients, during the study and to warrant adequate measures in case of safety concerns.

C

3.4 Rationale of dose/regimen, duration of treatment

Corporate Confidential Information

These dosing considerations are considered important because B cells residing in ectopic lymphoid tissues of pSS patients have been shown particularly resistant to depletion by rituximab, possibly due to the apoptosis resistant effects of high BAFF tissue levels associated with this disease process ([Pers et al 2007](#); [Quartuccio et al 2008](#); [Hamza et al 2012](#)). In addition, baseline serum levels of BAFF correlate inversely with duration of B cell depletion, with potential links to therapeutic efficacy of this approach ([Varin et al 2010](#)). Finally, the circulating B cell compartment is not representative of the tissue compartment where pathologic B cells are likely to reside,

C

Corporate Confidential Information
Corporate Confidential Information

3.5 Rationale for choice of comparator

In the current study, the placebo to VAY736 will be used as comparator to provide objective evidence of potential AEs and other safety data, as well as clinical efficacy and PD data generated from patients exposed to the experimental therapy during the initial 24-week trial. Since there is no established, clinically effective disease modifying treatment for patients with pSS, potential treatment with placebo is justified.

Furthermore, after unblinding, patients initially randomized to placebo will be offered optional treatment with a single administration of VAY736. The purpose of this optional open label administration of VAY736 is to allow all patients who participate in this study to have an equitable opportunity to eventually receive study drug.

3.6 Purpose and timing of interim analyses/design adaptations

An interim analysis is planned after all patients have completed the week 12 visit in order to assess the effect of VAY736 on the primary endpoints. For these subjects the efficacy endpoints up to week 12 (along with relevant safety data) will be examined as a preliminary evaluation of therapeutic effects.

In addition, an interim safety review will be performed between Cohort 1 and Cohort 2; details are given in [Section 3.1.1](#).

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.

Additional information is presented in [Section 9.8](#).

3.7 Risks and benefits

To date, no evidence-based, systemic therapy has been available for pSS patients. Corticosteroids and traditional disease modifying anti-rheumatic drugs have shown only modest effects, if any, on disease course. B cells have an established role in pSS pathogenesis, and potential benefits have been reported using the B cell depleting therapy rituximab in small numbers of pSS patients, with improvements observed in both glandular and extraglandular features ([Meijer et al 2010](#); [Meiners et al 2012](#)). Thus, therapies targeting B cells show promise in the treatment of pSS, although larger, confirmatory clinical studies remain to be done.

VAY736 is a B cell-depleting biologic of novel mechanism of action that has undergone limited phase I testing in RA patients, Corporate Confidential Information

This current study in pSS patients is designed to explore the clinical efficacy of VAY736 along with the safety, tolerability, PK and PD. VAY736 has never been used in patients with pSS and so no statement can be made of its efficacy in treating this disease.

By targeting the BAFF receptor, VAY736 incorporates dual mechanisms of action, including depletion of mature and immature B cells along with concurrent blockade of the maturation/survival pathway; biological effects that may be more efficacious for targeting the highly BAFF-driven, auto-reactive B cells underlying pSS pathogenesis. Corporate Confidential Information

3.7.1 Potential risks associated with exposure to VAY736

B cell depletion and blockade of BAFF signaling have been shown to be well-tolerated by patients with autoimmune diseases, including pSS patients, when therapeutically targeted independently. Experience with concurrent application of these mechanisms of action in humans has been limited to the phase I SAD trial of VAY736 in patients with active RA disease despite methotrexate treatment.

3.7.1.1 Cytokine release

Corporate Confidential Information

When large numbers of B cells are rapidly eliminated by ADCC, there is the potential for concurrent release of inflammatory cytokines. Infusion reactions have been experienced by over a third of RA patients exposed to rituximab despite receiving corticosteroid pre-medication ([Fleischmann 2009](#)), with a similar safety profile reported in rituximab-treated pSS patients ([Seror et al 2007](#); [Dass et al 2008](#)); ([Meijer et al 2010](#)). Corporate Confidential Information

3.7.1.2 Serum sickness

Primary Sjögren's syndrome patients treated with rituximab have also shown an increased incidence of serum sickness, with reported rates from 6-27% ([Pijpe et al 2005](#); [Seror et al 2007](#); [Dass et al 2008](#); [Meijer et al 2010](#)). Although the etiology of this reported increased susceptibility of pSS patients to serum sickness with rituximab remains unknown, the condition in humans is typically described as a type III, immune complex hypersensitivity reaction to proteins such as antibodies derived from animals. Although VAY736 is a fully human IgG monoclonal antibody, its potential for inducing serum sickness in pSS patients remains currently unknown.

3.7.1.3 Late onset neutropenia

More recently, late onset neutropenia (LON) is an increasingly recognized late adverse event of rituximab therapy, described primarily in oncology patients ([Tesfa and Palmblad 2011](#); [Wolach et al 2012](#)). The few available reports of late onset neutropenia in the treatment of autoimmune diseases, suggest that the incidence is comparable to that in the hematologic population (3-27%). LON has been reported to appear from 7-48 weeks following rituximab administration and to coincide with the time of B cell recovery. Cases typically self-resolve rapidly without the need for colony-stimulating factors and without significant morbidity or mortality. The specific cause of late onset neutropenia remains unknown and rechallenge with rituximab has not led to recurrent neutropenia in previously affected patients.

Corporate Confidential Information

One of 3 CLL patients receiving VAY736 in CVAY736Y2101 progressed from a base line grade 3 neutropenia to a non-study drug-related grade 4 neutropenia after four weekly doses of VAY736 0.002 mg/kg.

Corporate Confidential Information

3.7.1.4 Potential immune suppression effects

Infection

Corporate Confidential Information

Corporate Confidential Information In general, the risk of immune suppression is related to the intensity and duration of the immunosuppressive regimen administered. The expected extent and duration of circulating B cell depletion in patients exposed to VAY736 in this single dose, exploratory study is expected to be limited in comparison to patients receiving multiple cycles of rituximab.

Vaccinations

In immune suppressed patients, live vaccinations may cause serious adverse events and vaccination success may be attenuated. No data exists on the effect of VAY736 on response to vaccinations in general.

3.7.1.5 Administration of a monoclonal antibody

General risks associated with mAb administration in humans include the possibility of a hypersensitivity reaction characterized by acute or delayed allergic reaction, anaphylaxis, urticaria, rash, dyspnea, hypotension, fever, chills and immunogenicity. A serious infusion reaction that results in anaphylaxis is a rare event in monoclonal antibody therapy. VAY736 is a fully human mAb of the IgG1 class, and thus expected to be less immunogenic in humans than chimeric or humanized antibodies.

3.7.2 Risk of ultrasound contrast agent

The blood flow measurement and elastography of the parotid salivary glands by high-resolution ultrasound is optional

Corporate Confidential Information

The contrast agent SonoVue (sulphur hexafluoride microbubble, Bracco Imaging, Italy) is available only in EU. The contrast agent will be given intravenously to patients for ultrasound assessments.

SonoVue has a current marketing authorization from EMA. SonoVue is associated only with uncommon adverse effects. Adverse events associated with immune system disorders are not known in pre-marketing data.

Corporate Confidential Information

3.7.3 Pre-medication

Adverse effects from paracetamol at the dose to be administered is not expected.

Adverse effects from H1 receptor blockers (e.g., Fenistil™) at the dose to be administered are mild and include drowsiness and occasionally gastrointestinal disturbances, dryness of the mouth, vertigo excitation and headaches.

3.7.4 Risk mitigation strategy

This study is being initiated at hospital-based study sites with ready access to intensive care facilities for rapid assessment and treatment in the event of a VAY736-induced severe infusion reaction. The period during and immediately after (e.g., 2hr) the initial exposure to a biologic is the most critical for most infusion reactions (including hypersensitivity, cytokine release, anaphylaxis). To improve the safety margin in this study, we will administer VAY736 over a 1-2 hour period. During this time, the patient will be monitored closely by a physician with vital signs taken every 30 minutes. This would allow preventive measures to be taken if signs and symptoms indicate a reaction to the VAY736 infusion. In addition, all patients will receive pre-medication with paracetamol (and an H1 receptor blocker, if necessary) to diminish the signs and symptoms of infusion reactions. The subject will remain in the study center overnight post-infusion for observation and measurement of safety parameters. Additional precautionary safety measures will include staggering dosing of enrolled patients in the first cohort and the first 5 enrolled patients in the second cohort by a minimum of 20 hours.

The Sponsor and Principal Investigators will review cumulative, blinded safety data continuously and at scheduled quarterly meetings. Of note, the clinical safety plan for this study includes close monitoring by the investigator for signs of infection and of hematologic parameters that include neutrophil counts, and neutrophil parameters are included in the study entry criteria and stopping rules. The stopping criteria and guidelines ([Section 5.5.10](#)), in addition to the clinical opinion of the investigator, will be used in this phase IIa study for evaluating safety data. Although the stopping criteria will not incorporate an absolute requirement for causality, the potential relationship between an adverse event and VAY736 will be evaluated carefully on a case by case basis.

4 Population

Patients with active primary Sjögren's syndrome will be recruited. A total of around 26 subjects will be enrolled to participate in the study and to be randomized. At least 24 subjects are expected to complete the study.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria at screening and baseline. No additional criteria should be applied by the investigator in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all eligibility criteria at screening and study baseline. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study sites.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

Patients re-screening will be allowed in the study in the event of a delay in treatment, e.g., in the event a wash-out period of more than 28 days needs to be taken into consideration.

Patients, who were previously ineligible due to the autoantibody inclusion criterion that has subsequently been amended, may be re-screened to determine eligibility according to the updated inclusion criteria.

Patients that proceed to the open-label treatment arm of VAY736 will not be re-assessed for inclusion/exclusion criteria, other than clinical safety laboratory assessments, if clinically indicated.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill **all** of the following criteria at the time of screening and baseline evaluations unless otherwise noted:

1. Written informed consent must be obtained before any assessment is performed
2. Male and female subjects age 18 to 75 years of age included
3. Fulfilled revised European US consensus criteria for pSS ([Vitali et al 2002](#)); if key inclusion criteria are missing from medical history, information will be obtained at screening and may be used as a baseline value if required.
4. ESSDAI value ≥ 6 .
5. Elevated serum titers at screening of ANA ($\geq 1:160$) and of RF
OR
Seropositive at screening for anti-SSA (\pm anti-SSB) antibodies
6. Stimulated whole salivary flow rate at screening of > 0 mL/min
7. Subjects must weigh at least 50 kg and no more than 150 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 35 kg/m²
8. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Subjects fulfilling **any** of the following criteria are not eligible for inclusion in this study:
Corporate Confidential Information

2. Use of other investigational drugs at the time of randomization, or within 28 days or 5 half-lives of time of randomization, whichever is longer; or longer if required by local regulations.
3. Prior use of any B-cell depleting therapy (e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb)
4. Current use of prednisone > 10 mg/d or dose change within 2 weeks of the time of randomization
5. Prior treatment with any of the following within 180 days of randomization
 - Anti-BAFF mAb
 - CTLA4-Fc Ig (abatacept)
 - Anti-TNF- α mAb
 - Intravenous Ig
 - Plasmapheresis
 - i.v. or oral cyclophosphamide
6. Treatment with azathioprine, or prior use within 84 days of randomization; patients taking either hydroxychloroquine or methotrexate at a consistent dose for ≥ 3 months prior to randomization are eligible if dose is maintained throughout the study

Corporate Confidential Information

- 9. Active viral, bacterial or other infections at the time of screening or enrollment, or history of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms
Corporate Confidential Information
- 11. Receipt of live/attenuated vaccine within a 2 month period before enrollment
Corporate Confidential Information
- 13. History of primary or secondary immunodeficiency, including a positive HIV (ELISA and Western blot) test result
Corporate Confidential Information
- 17. History of hypersensitivity to drugs of similar chemical classes (e.g., IgG1 biologics) or to any of the constituents of the study drug (sucrose, L-Arginine hydrochloride, L-histidine, polysorbate 80, hydrochloric acid)
Corporate Confidential Information

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

The investigational drug, VAY736 vials will be packed by Novartis and supplied to the Investigator as open labeled bulk medication. The dosage form of the supplied drug is 150 mg lyophilisate in vial and needs to be reconstituted with water for injection (USP or equivalent) and diluted in 5% dextrose infusion bag (USP or equivalent), both may be provided by the investigator's site. Please refer to [Table 5-1](#) for VAY736 formulation information.

The placebo control selected for this study is the 5% dextrose solution in the infusion bag
Corporate Confidential Information

Bulk medication labels will be in the local language, will comply with the legal requirements of each country, and will include storage conditions for the drug but no information about the subject.

Clinical supplies are to be dispensed only in accordance with the specified study procedures.

An unblinded pharmacist or authorized designee is required to prepare the study drug. Instructions for storage and handling of VAY736 vials, and preparation of VAY736 and placebo infusions are described in the VAY736 Pharmacy Manual (or Dose Preparation Manual), provided as a separate document.

Corporate Confidential Information

5.1.2 Additional study treatment

5.1.2.1 Pre-medication

To attenuate severity of infusion reactions, all patients in both study arms should receive the following pre-medication regimen, provided by the study center, prior to the start of the infusion (VAY736 or placebo):

- 500 mg paracetamol p.o. 1 hour pre-dose and 5 hours [\pm 30 min.] post-dose and 1000 mg 11 hours [\pm 1 hour] post-dose.
- H1 receptor blockers (e.g., Fenistil™ [dimetinden] intravenously, dosed according to local prescribing standards) may be administered in the event paracetamol pre-medication does not prevent infusion reactions sufficiently. The decision may be made on a case-by-case basis or as a general recommendation if the paracetamol pre-medication is deemed not effective during conduct of the study.

5.1.2.2 Ultrasound i.v. contrast agent

To enhance echogenicity of the vasculature during high resolution, Doppler sonographic imaging of the parotid glands, contrast agent SonoVue (sulphur hexafluoride microbubble, Bracco Imaging, Italy) will be given to patients as an i.v. contrast agent for ultrasound assessments. This will permit quantitative measurement of parotid gland function

Corporate Confidential Information

SonoVue has a current marketing authorization from EMA for other indications. The ultrasound blood flow measurement is optional and will not be performed at study centers in countries where SonoVue is not available.

5.2 Treatment arms

In the first cohort, subjects will be randomized in a 2:1 ratio to one of the following 2 treatment arms, defined as:

- VAY736 active: single i.v. dose of 3 mg/kg VAY736 from infusion bag containing the active compound
- VAY736 placebo: single i.v. dose from infusion bag lacking active compound

In the second cohort, subjects will be randomized at a 6:1:3 ratio to one of the following 3 treatment arms, defined as:

- VAY736 active: single i.v. dose of 10 mg/kg VAY736 from infusion bag containing the active compound
- VAY736 active: single i.v. dose of 3 mg/kg VAY736 from infusion bag containing the active compound
- VAY736 placebo: single i.v. dose from infusion bag lacking active compound

Open label

Patients entering the open label cohort will be assigned to receive:

- VAY736 active: single i.v. dose of 10 mg/kg VAY736

5.3 Treatment assignment

Randomization numbers will be assigned in ascending, sequential order to eligible subjects (see [Section 5.5.1](#) for details). The investigator will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Novartis IIS Randomization Group.

Randomization numbers will be assigned in ascending, sequential order to eligible subjects (see [Section 5.5.1](#) for details). The investigator will enter the randomization number on the CRF.

Randomization Procedure for central management of randomization numbers:

When an eligible patient at a participating study site is ready to be randomized into the study, the steps below will be followed:

1. The site designee will complete a Randomization Request form and fax or email to the Novartis designee.
2. On receiving, the Novartis designee will write the next available randomization number within the randomization list for the corresponding part of the study on the form and fax or email back.
3. On receiving the allocated randomization number, the unblinded pharmacist or authorized designee will use the information on the completed form to ensure that the patient receives the correct study medication, according to the provided randomization list.
4. After inclusion of each new patient, the site designee will countersign the Randomization Request form, and fax or email it back to the Novartis designee to document the correct assignment of the patient's randomization number and the date the patient received their first dose of study medication.

5.4 Treatment blinding

This is a double blind study for the duration of the treatment period (Weeks 0-24), following which, treatment will be unblinded on an individual patient level to determine their progress in the study (follow-up, open-label VAY736 or End of Study Visit). Subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of study treatments according to the specifications provided in [Appendix 8](#). Randomization data are kept strictly confidential until the time of unblinding for the respective person(s). Further information regarding blinding (and unblinding) is presented in [Appendix 8](#).

The PK bioanalyst will be unblinded during the clinical study, but will not provide individual PK data until an IA or prior to data-base lock, to maintain the study blind.

In order to help reduce the risk of unblinding that might arise if an infusion reaction occurs, all patients will receive treatment with paracetamol (and a histamine H1 receptor blocker, if necessary) prior to infusion with VAY736.

Because the expected cell depleting effects of VAY736 will affect the patients' leukocyte counts and differentials, the hematology laboratory evaluation results will be concealed from the Investigators and patients in order to maintain the study blind (a separate study safety physician will review these results).

The necessary safety review may lead to the Novartis study team being inadvertently unblinded, however this information will not be communicated to the investigator.

An unblinded pharmacist at the investigator site will prepare the study treatment for infusion from the bulk open-labeled supplies. The diluent (dextrose 5% in water solution) serves as placebo and will not contain VAY736.

Further unblinding will only occur in the case of subject emergencies (see [Section 5.5.11](#)), at the time of an interim analysis and at the conclusion of the study.

5.5 Treating the subject

5.5.1 Subject numbering

Screening number

Each subject screened is assigned a unique screening number. The screening number is a combination of the center number that is provided by Novartis and a three digit number starting with 001 for each subject which is assigned by the Investigator. Therefore, if the center number is 1 (any leading 0's in the center number are dropped) the screening numbers will be assigned such as 1001, 1002, 1003 in ascending order. If the center number is 2 (or 0002), the screening numbers will be 2001, 2002, 2003 in an ascending order.

Randomization number

If the subject is deemed eligible for the study and will commence dosing, a randomization number will be assigned. Once assigned to a subject, a randomization number will not be reused.

The randomization number becomes the definitive subject number as soon as a subject receives the respective study treatment.

There should be a source document maintained at the site which links the screening number to the randomization number (once assigned). This source document should be provided to all appropriate parties (i.e., Central Laboratory, ECG Laboratory) as soon as this is available.

Randomization numbers will be generated for at least 26 subjects to allow for 24 subjects to complete the study. Subjects will be assigned randomization numbers, 5101-5106 in the first cohort and randomization numbers 5201-5222 in the second cohort. Replacement lists will be generated to replace early dropouts. Replacement subjects will be assigned randomization numbers 6101-6106 in the first cohort and 6201-6222 in the second cohort.

Placebo patients entering the open-label part cohort will be issued with a new randomization number. These patients will be assigned randomization numbers, 9101-9222. If a patient joins the open-label VAY736 part, the new randomization number assigned will correspond to the original randomization number (e.g. patients 5102 and 5211 would be assigned 9102 and 9211, respectively).

5.5.2 Dispensing the study treatment

The dosage form of the supplied drug is lyophilizate in vial and needs to be reconstituted with water for injection (USP or equivalent) and diluted in 5% dextrose infusion bag (USP or equivalent), both provided by the investigator's site. Please refer to [Table 5-1](#) for VAY736 formulation information. The placebo control selected for this study is the 5% dextrose solution in the infusion bag without addition of VAY736.

For preparation of the study medication, a copy of the randomization schedule will be sent to the unblinded pharmacist / technician at the Investigator's site or to the dispensing contractor.

Clinical supplies are to be dispensed only in accordance with the specified study procedures. Appropriate documentation of the subject specific dispensing process must be maintained.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the labels.

Storage conditions must be adequately monitored and appropriate temperature/humidity logs maintained as Source data.

The Investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the Monitor during site visits and/or at the completion of the trial.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply.

At the conclusion of the study, and, if allowed during the course of the study, the Investigator will provide a copy of the drug accountability ledger to the Monitor.

Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction or have the unused and partly used drug supplies as well as the empty containers destroyed by the site's pharmacist, providing a drug destruction certificate.

For more information on storage, handling and preparation of VAY736 vials and placebo infusions please refer to the Pharmacy Manual.

5.5.3.2 Handling of other study treatment

The following non-investigational treatment has to be monitored specifically:

- Use of pre-medication (paracetamol and the H1 receptor blocker (Fenistil™ [dimetinden], if applicable). For more information see [Section 5.1.2.1](#).
- SonoVue according to local standard

Details are described in the monitoring plan.

5.5.4 Instructions for prescribing and taking study treatment

VAY736 will be administered as an i.v. infusion over approximately 2 hours by the study center personnel following the instructions and using the material as described and specified in the VAY736 Pharmacy Manual. Any update to the Pharmacy Manual describing the preparation of additional doses will be provided as needed directly to the study center personnel.

A physician shall be available, e.g., by pager, DECT etc. at all other times throughout the study.

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

5.5.5 Permitted dose adjustments and interruptions of study treatment

If patients are unable to tolerate the protocol-specified dosing scheme, dose adjustments and/or interruptions are permitted. The following guidelines should be followed:

In case of suspected infusion reaction, the infusion can be stopped for 15 minutes and the patient observed to determine the severity of the reaction. Depending on the assessment of the patient, symptomatic treatment can be administered and the infusion can be restarted at a reduced rate if necessary.

In case of notable adverse events and/or safety concerns, the following changes to the planned dose of the next subject may be considered:

- Administration of a dose below the dose of 3 mg/kg or 10 mg/kg, respectively, after consultation between the sponsor and the principle investigator.

These changes must be recorded on the Dosage Administration Record CRF.

5.5.6 Recommended treatment of adverse events

The following guidelines are provided using the National Cancer Institute Common Toxicity Criteria for allergic reaction, anaphylaxis and cytokine release [NCI-CTCAE/v4.03, Reference <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>].

In the case of a suspected infusion reaction, the infusion can be stopped for 15 minutes and the patient observed to determine the severity of the reaction. Depending on the assessment of the patient, medication can be administered and the infusion can be restarted at a reduced rate if necessary.

Additional guidance on severity grading and treatment includes the following:

- Mild National Cancer Institute (NCI) grade 1 infusion reactions do not require treatment.
- In case of moderate NCI grade 2 infusion reactions requiring symptomatic treatment, the patient can be treated with anti-histamines, NSAIDs, paracetamol, intravenous fluids as determined by the investigator and the infusion can be stopped for 15 minutes and then restarted at a reduced rate.
- In case of more severe NCI grade 3 or 4 reactions, the infusion should be stopped and corticosteroids according to local guidelines administered intravenously.
- Other available medications at the bedside should include paracetamol, adrenaline, bronchodilators, and/or intravenous preparations of anti-histamines.

Infusion reactions of severity NCI grade ≥ 2 despite pre-medication with paracetamol and an H1 receptor blocker may require modification of the pre-treatment regimen. Medication to prevent or treat the signs and symptoms of infusion-related reactions will be provided by the study site.

Plasmapheresis may be helpful in situations in which decreasing the systemic concentration of VAY736 may be of clinical benefit, based on capacity of plasmapheresis to remove IgG antibody, such as the IgG monoclonal antibody VAY736, from intra- and extra-vascular compartments.

In the case of severe neutropenia requiring treatment, filgrastim (granulocyte colony - stimulating factor analog; G-CSF) may be used to stimulate the proliferation and differentiation of granulocytes.

In the case of clinically relevant hypogammaglobulinemia, an intervention may be required such as replacement by Intravenous Immunoglobulin (IVIG).

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

5.5.7 Rescue medication

There is no established, approved immunosuppressive treatment for pSS. Patients may receive NSAIDs, paracetamol, or symptomatic care at the discretion of the treating physician as outlined in [Section 5.5.8](#). Rescue medicine is to be provided by the study center or personal physician.

5.5.8 Concomitant treatment

Use of artificial tears and artificial saliva/salivary stimulants (e.g., cevimeline, pilocarpine) by the patient during participation in the protocol is permitted at the discretion of the treating physician. Amount and frequency of use should be recorded at each visit. Both treatment modalities are not permitted within 48 hours prior to, or during assessment of clinical disease outcome measurements. Artificial tears and artificial saliva are to be provided by the study center or personal physician.

The investigator should instruct the subject to notify the study site about any new medications he/she takes after the start of the study drug.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

5.5.9 Prohibited treatment

Use of the treatments displayed in the table below are NOT allowed after the start of study drug until week 24.

Table 5-2 Prohibited treatment

Medication	Action to be taken
Other experimental therapies	Withdrawal may be required on a case-by-case basis
Other biologics	Withdrawal may be required on a case-by-case basis
DMARDs or other immune suppressive agents or changes in an existing DMARD regimen (hydroxychloroquine or methotrexate)	Withdrawal may be required on a case-by-case basis
Regular, required treatment affecting exocrine gland function (including beta blockers, antihistamines, pseudoephedrine, selective antidepressants, anticholinergics, sedatives, antipsychotic drugs, anti- Parkinson agents, diuretics)	Withdrawal may be required on a case-by-case basis
Intermittent use may be allowed provided none of these drugs are taken within 5 half- lives of the drug in question before assessment at the major timepoints	

Patients who choose, subsequent to VAY736, therapy with another B-cell depleting agent (e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb) at any point during the study will be withdrawn from the safety follow up and will be requested to complete their EOS visit within 4 weeks.

5.5.10 Discontinuation of study treatment and premature subject withdrawal

Study “Stopping rules”

Corporate Confidential Information

However, infusion reactions (hypersensitivity, cytokine release, anaphylaxis) can occur with administration of biologics, in particular those which are lymphocyte-depleting by ADCC. Increased susceptibility to infection is also a potential risk with therapies targeting elements of the immune response. Thus, for patients on active treatment, the following guidance and stopping rules are provided.

Dose limiting toxicities (DLTs) will be assessed according to the standardized toxicity grading scale, the NCI Common Toxicity Criteria for Adverse Events [NCI-CTCAE/v4.03, Reference <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>]. Although the stopping criteria will not incorporate an absolute requirement for causality, the potential relationship between an adverse event and VAY736 will be evaluated carefully on a case-by-case basis.

Overall study:

The study will be put on hold pending further safety data analysis, if any of the following criteria occur in patients receiving VAY736:

- Any death
- Decrease in neutrophil count:
 - a. If any subject requires G-CSF or GM-CSF treatment for neutropenia, or
 - b. If two or more subjects manifest a persistent neutrophil count <500 cells/uL, or
 - c. If four or more subjects manifest a persistent neutrophil count <1000 cells/uL
- More than 1 infusion reaction of grade 3 severity of the NCI-CTCAE/v4.03 Criteria within the first 5 treated subjects or an incidence of >20% thereafter
- Any grade 3 toxicity of the NCI-CTCAE/v4.03 Criteria with the following exceptions:
 - Events of Special Interest, including infusion-related (hypersensitivity, cytokine release, anaphylaxis), decreased neutrophil or leukocyte counts not requiring treatment, and diagnostic procedures involving elective or non-urgent hospital admission
 - Disease Specific Events that are due to the patients underlying pSS diagnosis
 - AEs/SAEs clearly unrelated to the experimental compound as determined by the investigator or Novartis.
- Persisting NCI-CTCAE/v4.03 Criteria grade 3 or grade 4 changes from baseline in vital signs, electrocardiograms, or relevant, persistent changes in laboratory parameters, which are not consistent with existing co-morbidities or the desired mechanism of action of VAY736 (e.g., B cell depletion), in >1 patient within the first 5 treated subjects or an incidence of >20% thereafter
- Any NCI-CTCAE/v4.03 grade 4 event.

In addition, all blinded safety data, including events of special interest and disease specific events, will be evaluated by the Sponsor and PI continuously and at scheduled meetings. The study may be put on hold pending further data analysis, and the decision to adjust the dose or modify the pre-medication considered despite having not met the above listed criteria if the following additional criteria occur:

- The principal investigator or the Sponsor considers that the number and/or severity of AEs justify discontinuation of the study.
- Other clinically significant changes or effects in the opinion of the Investigator or Sponsor that are deemed unsafe to continue dosing.

This study can also be terminated at any time for any reason by Novartis. Should this be necessary, the Investigator will be informed of the procedures to be followed to assure that adequate consideration is given to the protection of the patients' interests. The Investigator will be responsible for informing the IEC/IRBs of the early termination of the trial.

Individual subject withdrawal

Due to the single dose nature of this study, no individual treatment stopping rules are provided.

Subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If a subject withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's withdrawal from the study and record this information on the CRF.

Patients that become pregnant during the study should be followed up as per the [Assessment schedule](#). The investigator may determine whether any assessments should not be performed if they are considered to not be clinically appropriate, in conjunction with the patients treating physician/obstetrician.

Patients who choose, subsequent to VAY736, therapy with another B-cell depleting agent (e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb) at any point during the study will be withdrawn from the safety follow up and will be requested to complete their EOS visit within 4 weeks.

If evidence of a clinically relevant acute infection is present before administration of an infusion of VAY736, the patient should not receive the infusion. Patient can be considered for later administration of VAY736 if infection is completely resolved within the screening period or upon re-screening.

Patients who withdraw before week 12 or between week 12 and week 24, should return for the long-term follow up period at week 12 or at week 24, respectively where they will have visits according to the following schedule until their B cell count is within the recovery threshold criteria:

- Every 4 weeks until the week 24 visit
- Every 8 weeks until the week 40 visit
- Every 12 weeks until the week 52 visit
- Every 24 weeks until the week 100 visit
- Every 48 weeks thereafter

Once B cell recovery threshold criteria are met, the patients will undergo the End of Study visit within 4 weeks. The End of Study visit will include study completion evaluations followed by discharge from the study.

Patients who discontinue during the safety follow up period will be asked to complete the end of study visit.

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

5.5.11 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code should not be recorded on the CRF.** The investigator must also immediately inform the Novartis local monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IVRS/IWRS/code break cards in case of emergency. If appropriate, the investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable.

An assessment will be done by the appropriate site personnel and the sponsor after an emergency unblinding to assess whether or not the patient should be withdrawn from the study.

5.5.12 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. The study will complete when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

After study participation, the patients will continue to be treated by his/her general practitioner according to the local standard clinical management related to the underlying disease.

5.5.13 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit assessments

The full [Assessment schedule](#) is presented at the end of the synoptic section, above.

Subjects should be seen for all visits on the designated day, or as close to it as possible. For study visit Day 7, a visit window of ± 1 day is acceptable, and for study visits Day 14 and Day 21, a visit window of ± 2 days is acceptable. For study visits Day 42, Day 63, Day 84, Day 112, Day 140 and Day 168, a visit window of ± 4 days is acceptable. For the follow-up visits, a time window of ± 2 weeks is accepted. For ultrasound assessments, a window of ± 7 days will be acceptable. The End of Study visit will be done within 6 weeks after the previous visit.

Subjects who discontinue study treatment before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. For safety reasons, patients should continue to be evaluated for safety/PK/PD parameters according to protocol, up to the study completion visit.

Deviations for the following PK assessment times are acceptable based on logistical and operational considerations:

PK assessments post VAY736 infusion of ± 15 minutes up to the first 24 hrs, ± 1 hour up to day 7, and ± 2 days thereafter. However, the 1-2h post-dose PK sample may deviate more than the allowed 15 min. as it must by definition be taken at the end of the infusion period.

Every effort will be made to take the pharmacokinetic sample at the protocol specified time. Other assessments, e.g., ECG, vital signs etc. will be taken after the pharmacokinetic sample.

When the following assessments are scheduled to be performed at the same time-point, the order of priority will be as follows:

1) PK specimen; 2) Blood sample for flow cytometry panels; 3) Hematology specimen; 4) BAFF blood specimen; 5) other BM specimens; 6) Chemistry specimen; and 7) other remaining laboratory and clinical assessments.

Should it become necessary to repeat an evaluation (e.g., ECGs, laboratory tests, vital signs, etc.), the results of the repeat evaluation should be captured. The additional assessment will be entered in the 'Unscheduled Visit' (e)CRF page provided in the (e)CRF.

6.1 Dietary, fluid and other restrictions

Subjects should maintain their usual diet and life habits during the entire study while not domiciled.

Intake of medications known to cause dry mouth / eyes as a major side effect should be interrupted five half-lives prior to efficacy assessments at baseline and on Day 42 (week 6), Day 84 (week 12), Day 168 (week 24) and at the end of study.

6.2 Subject demographics/other baseline characteristics

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, the diagnosis and not symptoms will be recorded.

The date of original diagnosis of primary Sjögren's syndrome has to be recorded.

Hepatitis screen, HIV screen

All subjects will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot. Appropriate subject counseling will be made available by the Investigator in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

Results will be available as source data and will not be recorded within the (e)CRF.

Alcohol test, Drug screen

Subjects will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates).

Results will be available as source data and will not be recorded within the (e)CRF.

Corporate Confidential Information

6.3 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with VAY736, as detailed in [Section 6.6](#).

6.4 Efficacy / Pharmacodynamic assessments

In addition to assessments for safety, PK and PD, exploratory clinical efficacy measurements will include components of the ESSDAI and of the ESSPRI and other patient-based assessments, along with imaging, histopathology and functional assessments of the exocrine glands. Soluble markers of B cell activation and flow cytometry analysis of B cell subsets will also be performed.

6.4.1 ESSDAI

The ESSDAI ([Appendix 3](#)) is an established disease outcome measure for Sjögren's syndrome that will be applied to the study patients at baseline and again at weeks 6, 12 and 24.

The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score.

6.4.2 ESSPRI

The ESSPRI ([Appendix 4](#)) is an established disease outcome measure for Sjögren's syndrome that will be applied to the study patients at baseline and again at weeks 6, 12, 24 and EOS for patients who do not meet end of study criteria at week 24.

6.4.3 SF-36

The Short Form (36) Health Survey (SF-36) is a survey evaluating individual patients' health status which also monitors and compares patients' disease burden.

The SF-36 consists of eight scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health), which are the weighted sums of the questions in their section.

It will be applied to the study patients at baseline and again at weeks 6, 12, 24 and EOS for patients who do not meet end of study criteria at week 24.

6.4.4 MFI

The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report instrument designed to measure fatigue covering the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. It will be applied to the study patients at baseline and again at weeks 6, 12, 24 and EOS for patients who do not meet end of study criteria at week 24.

6.4.5 Global assessments (VAS) of disease activity

6.4.5.1 Physician's global assessment

The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question "Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her

condition is today". The investigator will then measure the distance in mm from the left edge of the scale and the value will be entered on the eCRF.

6.4.5.2 Patient's global assessment

The patient's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question on how well the patient is doing with the disease considering all aspects affected by the disease. The investigator will then measure the distance in mm from the left edge of the scale and the value will be entered on the eCRF.

6.4.6 Selective depletion of B cells

Depletion of B cells will be evaluated by measuring absolute counts of CD19+ B cells by flow cytometry. Additional detail of this depletion will be obtained using a more detailed B cell subset panel. The selectivity of B cell depletion will be demonstrated by measuring absolute counts of other leukocyte subsets.

Patients need to achieve B cell recovery to complete the study.

When patients reached week 24, the following definition of B cell recovery was applied to determine whether a long-term safety follow up would be required: B cells [CD19+] returning to within 20% of baseline or ≥ 80 cells μL .

Following Amendment 05 to the protocol, the cut-off used as a criterion to define B-cell recovery during long term follow-up (starting week 32) was decreased to within 20% of baseline or ≥ 50 cells/ μL based on published experience with ocrelizumab for which 95% (n=237) of RA patients had a CD19+ B cell count ≥ 40 cells/ μL at all available pre-treatment visits ([Genovese et al 2008](#)).

6.4.6.1 Pharmacodynamic sample collection and processing

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. For each scheduled visit, one 2.6 mL blood sample will be collected in Na-heparin Monovette tubes by aspiration.

From the 2.6 ml blood 4 different assays will be performed:

- Immunophenotyping panel: absolute counts of leukocyte subsets (safety markers, [Section 6.5.4.2](#)) including CD19+ B cells (PD marker)
- Lymphocyte activation panel: activation of lymphocytes ([Section 6.5.4.2](#))
- B cell subset panel ([Section 6.8.2.1](#))
- Additional flow cytometry panels may also be performed.

Optional specimen (approximately 2.6 mL): Chemokine receptor expression panel. Sample collection and processing will follow the local requirements.

For the Immunophenotyping, Lymphocyte activation, B cell subset and additional flow cytometry panels 2.6 ml blood need to be distributed on 4 tubes. Antibody mixes and lysis buffer needs to be added to the tubes and tubes should be frozen at -80°C as described in detail in a separate lab manual provided by BMD, Novartis.

For detailed description of blood sampling schema, please refer to the Blood Log in [Appendix 1](#).

Detailed information on sample collection, handling and shipment will be provided in a separate laboratory manual.

6.4.7 Ultrasound assessments

All patients will undergo assessment by high resolution ultrasound (5 – 14 MHz transducer frequency) according to the schedule. The ultrasound protocol will include B-mode assessment of both left and right parotid and submandibular glands to determine gland thickness (mm) and Sjögren's ultrasound disease staging ([De Vita et al 1992](#)).

At study centers located in countries where SonoVue is available, subject may also be assessed for salivary gland (parotid gland only) blood flow and regional blood volume on both left and right parotid gland, each after receiving contrast agent. A total of 2 maximum, approximately 2.4-ml contrast bolus injections of SonoVue (sulphur hexafluoride bubbles; Bracco, Milan, Italy) contrast agent into a peripheral vein (e.g., a cubital vein). Regions of interest will be placed on the parotid gland and estimates of contrast agent influx and area under the curve (AUC) will be calculated.

Corporate Confidential Information

Each ultrasound assessment visit will last for approximately 30 minutes.

Detailed information will be provided in a separate Ultrasound manual.

6.4.8 Assessment of salivary flow

Both the amount and composition of saliva has been shown to reflect the damage caused by the disease process of Sjögren's syndrome ([Pijpe et al 2006](#)). Unstimulated and stimulated whole and/or glandular salivary fluid is obtained from patients at screening to evaluate eligibility (stimulated only) and at each clinical disease assessment time point (baseline and weeks 6, 12 and 24). Patients are instructed not to eat, drink or smoke for 90 minutes before assessment of salivary flow. All assessments are performed at a fixed time of the day to minimize fluctuations related to the circadian rhythm of salivary flow and composition.

Unstimulated and stimulated salivary secretions are collected over 5 minutes.

The following saliva collection methods may be utilized following the manufacturers' instructions:

- Passive drool collected using a Saliva Collection Aids (SCA) constructed of polypropylene (e.g., Salimetrics Part no. 5016.02)
- Oral cotton swabs (e.g., Salimetrics Oral Swabs or Salivettes)
- Cotton swabs containing citric acid solution (2% st/vol)

Additional material may be used following appropriate procedures. For more details refer to the laboratory manual.

Saliva collected under unstimulated conditions may also be used for the assessment of saliva composition.

The start time and end time of saliva collection will be recorded to calculate the salivary flow rate.

The same method of saliva collection and salivary flow rate determination should be used for an individual patient at each assessment time point and for each purpose, respectively.

6.4.9 Ocular Staining Score

Corneal fluorescein staining pattern (step 1 of the OSS scoring system)

Each cornea is examined at the slit lamp using the cobalt blue filter. Grading of the fluorescein pattern is initiated between 4 and 8 minutes after instillation of fluorescein. Punctate epithelial erosions (PEEs) that stain with fluorescein are counted and scored ([Whitcher et al 2010](#); see [Appendix 7](#) for grading of the scored PEEs). An additional point is added if: (1) PEE occurred in the central 4-mm diameter portion of the cornea; (2) one or more filaments is seen anywhere on the cornea; or (3) one or more patches of confluent staining, including linear stains, are found anywhere on the cornea. The total fluorescein score for the cornea (the PEE grade plus any extra points for modifiers) is noted in the central square of the SICCA ocular staining score form. The maximum possible score for each cornea is 6.

Conjunctival lissamine green staining pattern (step 2 of the OSS scoring system)

After the external examination, 1 drop of 1% lissamine green dye is applied to the inferior conjunctival fornix of both eyes. Alternatively, lissamine green stripes can be used and placed in the inferior conjunctival fornix of both eyes. The same method of administering lissamine green should be used for an individual patient at each assessment time point. The conjunctivae are examined with the slit lamp at x10 magnification, using a neutral density filter over the light source to avoid blanching of the conjunctiva. It is important to examine and grade the eyes immediately after instilling lissamine green dye because the intensity and extent of the ocular staining diminishes rapidly after the first 2 minutes. It is also important for the patient to blink several times to keep dye from pooling in the conjunctival folds which can mimic conjunctival staining. If adequate dye is not instilled initially, a second drop can be given and the examination performed immediately thereafter. The number of dots is counted (see [Appendix 7](#) for grading of the scored dots; nasal and temporal bulbar conjunctivae graded separately). Because of the difficulty of counting individual dots in a moving eye at the slit lamp, any area of confluent staining of 4 mm² or more is considered to be more than 100 dots. Nasal and temporal areas of the conjunctiva are graded separately with a maximum score of 3 for each area or a total maximum score of 6 for each eye (nasal plus temporal).

Calculation of total OSS

The total OSS for each eye is the summation of the fluorescein score for the cornea and the lissamine green scores for the nasal and temporal bulbar conjunctiva. The maximum possible score for each eye is 12.

6.5 Safety

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded in the CRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History CRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event CRF.

6.5.2 Vital signs

Vital signs include blood pressure (BP), pulse measurements, and body temperature. After the subject has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening and/or at baseline, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol-specified ranges, the subject is excluded from the study.

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range for the laboratory at screening and/or baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured.

6.5.4.2 Leukocyte subsets and lymphocyte activation

Two flow cytometry-based panels will be conducted on whole blood for monitoring the response of circulating leukocytes to VAY736 exposure as well as the activation status of lymphocytes:

Corporate Confidential Information

Blood for these safety flow cytometry panels will be collected together with the blood for the PD (B cells depletion) assessment in the same tube ([Section 6.8.2.1](#)).

Detailed description on splitting the blood for the three assays as well as further information on sample processing (assay procedure) is given in a separate lab manual provided by BMD, Novartis.

6.5.4.3 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO₂, calcium, cholesterol, chloride, creatinine, CK, CRP, γ -GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN and uric acid.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

6.5.4.4 Urinalysis

A midstream urine sample (approximately 30 ml) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative “dipstick” evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for protein, nitrite, leukocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

6.5.4.5 Special clinical laboratory evaluations

Serum markers of B cell hyperactivity can be present in pSS and may be affected by depletion of B cells.

Corporate Confidential Information

6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed in lying position. Interpretation of the tracing must be made by a qualified physician and documented on the ECG / in the ECG section of the eCRF. Each ECG tracing should be labeled with the

- study number
- patient initials
- patient number
- date

and kept in the source documents at the study site. Clinically significant abnormalities should be recorded on the relevant medical history/Current medical conditions CRF page prior to informed consent signature and on the Adverse Events page thereafter. Clinically significant findings must be discussed with the sponsor.

The CRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QTcF interval calculated by ECG machine
- QRS duration

The overall interpretation will be collected with a Yes/No statement to confirm if any clinically significant abnormalities are present which need to be specified further.

Original ECG tracings, appropriately signed, will be archived at study site.

6.5.6 Pregnancy

Pregnancy tests are required of all female subjects regardless of reported reproductive / menopausal status.

Serum pregnancy tests will be performed at screening; at all other times urine pregnancy tests may be used.

If a urine pregnancy test is performed and is found to be positive, this will require immediate performing a serum β -hCG. If positive, the sponsor and investigator will decide if discontinuation from the trial is required or whether study assessments can continue without compromising the patient's safety.

When performed at screening and at baseline, the result of this test must be received before the subject may be dosed.

6.5.7 Other safety assessments

6.5.7.1 PPD skin test or QuantiFeron test

A purified protein derivative (PPD) skin test will be performed and read at screening or within 6 months prior to randomization in order to evaluate an eventual infection with tuberculosis (TB). The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD injected intradermally into usually the volar surface of the forearm. The site is cleansed and the PPD extract is then injected into the most superficial dermal layer of the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the subject must return to the investigators' site within that time for a proper evaluation of the test site. This will determine whether the subjects have had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥ 5 mm is interpreted as positive result.

Precautions against tuberculosis should be handled according to the best medical practice consistent to the local standards in each country with prior consultation with Novartis. Patients requiring administration of antibiotics against latent tuberculosis should complete their treatment and should be considered cured prior to being re-considered for entry into this study (consultation with Novartis must occur before allowing the patient to enter the study).

Based on the study site's normal practice, QuantiFeron test may replace PPD skin test at screening. A positive QuantiFeron test at screening will exclude the subjects from the participation in the study.

Results will be available as source data and will not be recorded within the (e)CRF.

6.5.7.2 Infections

All occurrences of infections must be carefully monitored by the investigator. Significant findings, which meet the definition of infection, must be recorded in the Adverse Event (e)CRF.

6.6 Pharmacokinetic assessments

See Sample log tables [Section 13-Appendix 1](#).

6.6.1 PK Blood collection and processing

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. 3.0 mL of blood will be collected into plain barrier (Serum Separator) tubes (no anti-coagulant) to obtain approximately 1.3 mL serum.

Blood samples will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum and then centrifuged for 15 minutes at approximately 1500 g at room temperature (or sufficient time and force to achieve a clear serum layer above the red cell clot). The serum samples will be placed on dry ice, split into 2 aliquots, transferred into labeled freezer-proof clear polypropylene screw-cap tubes and then stored (within 1 hour of serum collection) at or below -70°C pending shipment. All samples will be given a unique

sample number and a collection number (as listed in the blood log [Appendix 1](#)). Further details on labeling of the PK samples and shipment instructions will be provided in a separate laboratory manual. The exact clock time of dosing, as well as actual sample collection date and exact time will be entered on the PK blood collection summary page of the eCRFs. Sampling problems will be noted in the Notes field of the eCRFs.

Corporate Confidential Information

6.6.3 Pharmacokinetic parameters

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters of VAY736 will be determined using the actual recorded sampling times and non-compartmental method(s) with WinNonlin Phoenix (Version 6.2 or higher): C_{max}, T_{max}, AUC_{last}, AUC_{inf}, T_{1/2}, V_z and CL from the plasma concentration-time data.

Concentrations below the LLOQ will be treated as zero for PK parameter calculations. The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T_{1/2} will include at least 3 data points after C_{max}. If the adjusted R² value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T_{1/2}, AUC_{inf}, V_z and CL.

Corporate Confidential Information

Refer to the [Assessment schedule](#) table, for the time schedule for pharmacogenetic blood sampling.

6.8.2 Other biomarkers

Corporate Confidential Information

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Pre-existing medical conditions/diseases (i.e., Medical History[ies]) are considered AEs if they worsen after providing written informed consent. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, or are considered clinically significant, or they require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

All adverse events will be reported from the time the subject has provided informed consent to visit 16 (week 52). Starting from visit 17 until end of study, only AE related to VAY736 as assessed by the investigator and AE related to infection, potential malignant events and neutropenia will be recorded (only valid for AE, not for SAE).

Adverse events must be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the CTC-AE grade
 - If CTC-AE grading does not exist for an adverse event, use 1=mild; 2=moderate, 3=severe; and 4=life threatening. CTC-AE grade 5 (death) is not used, but is collected in other CRFs (e.g., Study Completion, Death/Survival).
2. its relationship to study treatment
3. its duration (e.g., start and end date)
4. whether it constitutes a serious adverse event (SAE)
5. action taken regarding study treatment
6. whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
7. its outcome

An SAE is defined as any AE which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see [Section 7.2](#).

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the informed consent and should be discussed with the subject during the study as needed.

7.2 Serious adverse event reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the subject has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is the later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow-up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the OC/RDC system (where available). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and also a copy to the Novartis Translational Medical Expert and Clinical Trial Leader (according to [page 2](#)). The telephone and fax numbers of the contact persons in the local Drug Safety and Epidemiology department, specific to the site, are listed on [page 2](#) of this protocol and/or in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

SAEs (initial and follow-up) that are recorded *electronically* in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Novartis Translational Medical Expert and Clinical Trial Leader (according to [page 2](#)).

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of liver function test (LFT) elevations
- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs and/ or pre-specified adverse events.

Please refer to [Appendix 2](#) for complete definitions of liver events.

Any liver event which meets the criteria for a “**medically significant**” event should follow the **standard procedures for SAE reporting** as described in [Section 7.2](#).

Every liver event as defined in [Appendix 2-Table 14-1](#) should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in [Appendix 2-Table 14-2](#).

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution

These investigations can include serology tests, imaging and pathology assessments, hepatologist’s consultancy, based on investigator’s discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF.

7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.5 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before

transfer of the data to Novartis or the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

All data captured for this study will have an external originating source (either written or electronic), the CRF is not considered as source.

8.3 Database management and quality control

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Novartis staff or CRO working on behalf of Novartis will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be sent (e.g., fax, e-mail) to the site. Site personnel will complete and sign the copy, then send it (with original signature) back to Novartis staff who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples

Corporate Confidential Information

will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug dispensed to the subject and all dosage changes will be tracked. The database managed by a vendor will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

Each occurrence of a code break will be reported to the clinical team and monitor. The possibility to break the code will remain available until study shut down or upon request of Novartis.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The full analysis set will include all subjects that received any study drug.

The safety analysis set will include all subjects that received any study drug.

The primary PK analysis set will include all subjects with available PK data. The secondary PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

9.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration and concomitant therapies will be listed by treatment group and subject.

9.4 Analysis of the primary variable

The primary aim of this study is to evaluate the effect of a single i.v. dose VAY736 on the clinical disease activity of primary Sjögren's syndrome patients as measured by the ESSDAI at week 12 compared to baseline. The statistical analysis model will include data on the ESSDAI from all timepoints at which it was recorded (baseline, weeks 6, 12 and 24) but the primary comparison is made for week 12.

Summaries of safety and tolerability data to support the second primary objective will be provided as detailed in [Section 9.5.2](#).

9.4.1 Variable(s)

The primary efficacy variable is the ESSDAI recorded at baseline and week 12.

9.4.2 Statistical model, hypothesis, and method of analysis

It is assumed that the ESSDAI will follow an approximate normal distribution. If, on blinded review of the data, this assumption appears to not be met, alternative statistical methods may be applied. These will be described full in the Reporting and Analysis Plan (RAP).

A positive sign of therapeutic effects will be considered to be a difference of at least 5 points in the change from baseline between VAY736 and placebo with a moderate level of evidence. Additionally there should be a high level of evidence that is a difference between VAY736 and placebo. The two active doses will be pooled for the primary efficacy analysis (unless there is evidence of inferiority of the 3 mg/kg dose to the 10 mg/kg dose). These criteria will be evaluated by calculating Bayesian posterior probabilities as follows:

$$\Pr(\theta_{\text{VAY736},12\text{w}} - \theta_{\text{placebo},12\text{w}} > 0 \mid \text{data}) > 90\% \text{ and}$$

$$\Pr(\theta_{\text{VAY736},12\text{w}} - \theta_{\text{placebo},12\text{w}} > 5 \mid \text{data}) > 50\%$$

where θ means change from baseline in ESSDAI at 12 weeks.

It is assumed that Y_{ijt} , the observed change from baseline in ESSDAI for subject i receiving treatment j (VAY736 or placebo) at time t , follows a normal distribution $N(\theta_{jt}, \sigma^2)$. It is further assumed that θ_{jt} follows a standard non-informative prior Normal distribution, $p(\theta_{jt}, \sigma^2) = 1/\sigma^2$.

The statistical model will include terms for the patient effect (as a random effect), treatment effect, post-baseline time (as nominal study week), the interaction between time and treatment (all as fixed effects) and with the baseline ESSDAI as a covariate.

Estimates of the difference between VAY736 and placebo at each timepoint will be derived from this model and presented together with 95% credible intervals.

The estimates of the posteriors probabilities of the efficacy criteria being met will be provided.

For the interim analysis planned when all patients have completed the week 12 visit, the same statistical methods will be applied and the results compared to the specified efficacy decision criteria.

9.4.3 Handling of missing values/censoring/discontinuations

Patients with missing ESSDAI at baseline will not be included in the analysis. Patients with missing data at one or more timepoints post baseline will be included in the analysis. The planned mixed effects model assumes that missing values are missing at random. The reasonableness of this assumption will be checked during the blinded review of the data and if necessary further methods may be applied.

9.4.3.1 Supportive analyses

The primary analysis uses a standard mixed model repeated measures approach where timepoints are considered as factors. This was chosen since the time course of ESSDAI changes following a single dose of VAY736 or placebo is not known. Supportive analyses will attempt to model the time effect to better describe changes over time.

Potential differences in efficacy between the 3 mg/kg dose and the 10 mg/kg dose of VAY736 may be explored.

9.5 Analysis of secondary and exploratory variables

9.5.1 Efficacy / Pharmacodynamics

Secondary efficacy variables supporting the exploratory objectives are:

- EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI) change from baseline.
- Change in physician global assessment of the patient's overall disease activity between baseline and week 12 as recorded by a visual analog scale (VAS)
- Change in the patient's global assessment of their disease activity between baseline and week 12 as recorded by a VAS
- Change from baseline for each domain of the Short Form (36) Health Survey (SF-36).
- Change from baseline for each dimension of the Multidimensional Fatigue Inventory (MFI) Questionnaire.

The secondary efficacy variables will be analyzed following the same approach used for the primary efficacy variable.

Corporate Confidential Information

- Salivary flow rates
- Ocular Staining Score

Corporate Confidential Information

- Serum levels of B cell activation markers, Corporate Confidential Information

Corporate Confidential Information

- Leukocyte subsets and lymphocyte activation markers
Corporate Confidential Information

Further definition of these exploratory variables and the statistical analysis methods will be described in the RAP.

9.5.2 Safety

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data, including pregnancy tests, will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

9.5.3 Pharmacokinetics

VAY736 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be calculated as described in [Section 6.6.3](#) and will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is T_{max} where median, minimum and maximum will be presented.

Modeling of the PK data may be performed as appropriate. During modeling of the pharmacokinetics of the study drug, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics will be followed. Subjects with missing PK parameters (e.g., C_{max}, AUC_{last}, AUC_{inf}) in some but not all periods will be included in a mixed model analysis assuming missing at random.

9.5.4 Pharmacokinetic / pharmacodynamic interactions

PK/PD modeling will be used to explore the relationship between extent and duration of B cell depletion and the pharmacokinetic profile of VAY736.

Corporate Confidential Information

9.5.7 Other biomarkers

All biomarker data will be listed by treatment, subject, and visit/time. Summary statistics will be provided by treatment and visit/time.

In the summary tables, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.

In case of censored values (values below the LLOQ and/or values above the ULOQ), the summary statistics (arithmetic mean, standard deviation, geometric mean and CV% of geometric mean) will be calculated as the maximum likelihood estimates using a parametric model for data that can be right censored and left censored assuming the data being normally or log-normally distributed.

9.6 Sample size calculation

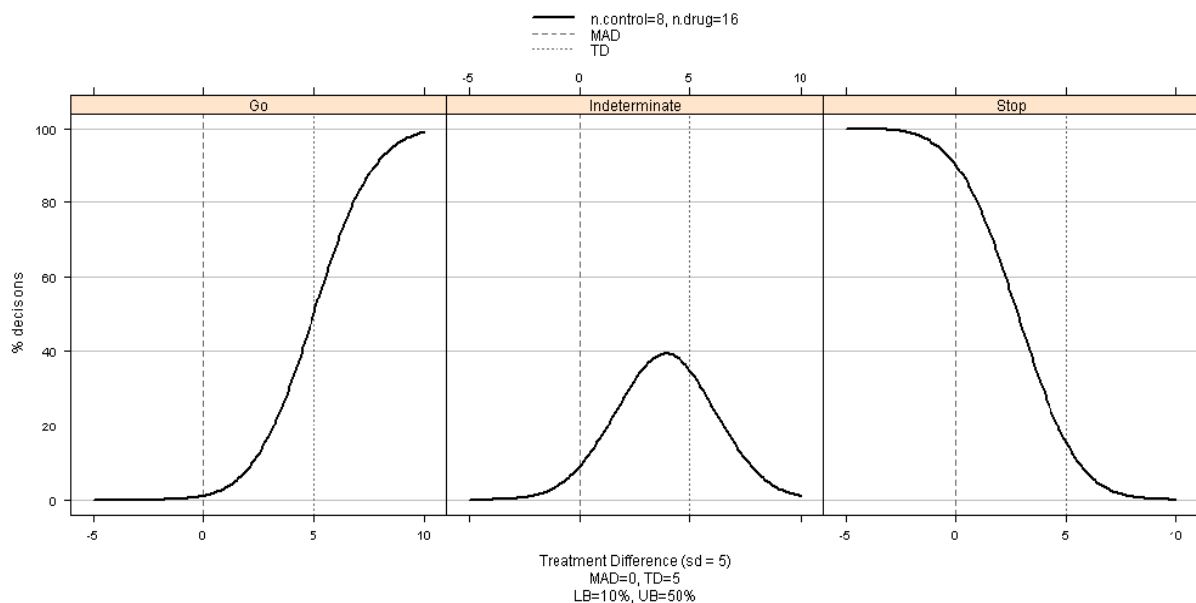
The sponsor is targeting to enroll around 26 patients in this study (with replacement strategy) and expects at least 24 patients to complete the assessments. With 24 patients in the analysis of the primary efficacy variable (assuming 16 in the VAY736 group and 8 in the placebo group), the study would have around 1% chance of having a false-positive result, i.e., of meeting both the efficacy criteria when the true difference between VAY736 and placebo is zero. Additionally the chances of meeting both the efficacy criteria remain below 20% for true differences between VAY736 and placebo of less than 2 points.

The study would have approximately 80% chance of meeting both the efficacy criteria, when the true difference between VAY736 and placebo is 7 points.

These calculations assume that the primary efficacy variable, ESSDAI, follows a normal distribution with a standard deviation of 5. This estimate of the standard deviation is based on a study of rituximab in patients with primary Sjögren's syndrome ([Meiners et al 2012](#)) in which the observed standard deviation at baseline ranged from 5 at baseline to 3-7 after study.

The figure below (Figure 9-1) shows the chances of meeting the efficacy criteria (shown as “Go” in the figure), or of meeting one of the two criteria (shown as “indeterminate”) or of not meeting the efficacy criteria (shown as “Stop”) for different true differences between VAY736 and placebo.

Figure 9-1 Probability of meeting efficacy criteria for N=16:8 VAY736:placebo



9.7 Power for analysis of key secondary variables

Not applicable.

Corporate Confidential Information

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

Corporate Confidential Information

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for subject safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the Health Authorities (where required) and the IRB/IEC/REB at the study site should be informed within 10 working days or less, if required by local regulation.

12 References

Available upon request.

Bourre-Tessier J, Haraoui B (2010) Methotrexate drug interactions in the treatment of rheumatoid arthritis: a systematic review. *J Rheumatol*; 37:1416-1421.

Cambridge G, Leandro MJ, Edwards JCW, et al (2003) Serological changes following B lymphocyte depletion therapy for rheumatoid arthritis. *Arthritis Rheum*; 48:2146-2154.

Chisholm DM, Mason DK (1968) Labial salivary gland biopsy in Sjögren's disease. *J Clin Pathol*; 21:656-660.

Dass S, Bowman SJ, vital EM, et al (2008) Reduction of fatigue in Sjogren's syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. *Ann Rheum Dis*; 67:1541-1544.

De Vita S, Lorenzon G, Rossi G, et al (1992) Salivary gland echography in primary and secondary Sjögren's syndrome. *Clin Exp Rheumatol*; 10:351-6.

Fleischmann RM (2009) Safety of biologic therapy in rheumatoid arthritis and other autoimmune diseases: focus on rituximab. *Semin Arthritis Rheum*; 38:265-280.

Genovese MC, Kaine JL, Lowenstein MB, et al (2008) Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis. *Arthritis Rheum* 58:2652-61.

Greenspan JS, Daniels TE, Talal N, et al (1974) The histopathology of Sjögren's syndrome in labial salivary gland biopsies. *Oral Surg*; 37:217-229.

Hamza N, Bootsma H, Yuvaraj S, et al (2012) Persistence of immunoglobulin-producing cells in parotid salivary glands of patients with primary Sjögren's syndrome after B cell depletion therapy. *Ann Rheum Dis*; (epub ahead of print)

Marco H, Smith RM, Jones RB, et al (2014) The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. *BMC Musculoskeletal Disorders*; 15:178.

Meijer JM, Meiners PM, Vissink A, et al (2010) Effectiveness of rituximab treatment in primary Sjögren's syndrome. *Arthritis Rheum*; 62:960-968.

Meiners PM, Arends S, Brouwer E, et al (2012) Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. *Ann Rheum Dis*; 71:1297-1302.

Mikuls TR, O'Dell JR, Stoner JA, et al (2004) Association of rheumatoid arthritis treatment response and disease duration with declines in serum levels of IgM rheumatoid factor and anti-cyclic citrullinated peptide antibody. *Arthritis Rheum*; 50:3776-3782.

Pers JO, Devauchelle V, Daridon C, et al (2007) BAFF-modulated repopulation of B lymphocytes in the blood and salivary glands of rituximab-treated patients with Sjögren's syndrome. *Arthritis Rheum*; 56:1464-1477.

Pijpe J, van Imhoff GW, Spijkervet FKL, et al (2005) Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. *Arthritis Rheum*; 52:2740-2750.

Pijpe J, Kalk WWI, Bootsma H, et al (2006) Progression of salivary gland dysfunction in patients with Sjögren's syndrome. *Ann Rheum Dis*; 66:107-112.

Quartuccio L, Fabris M, Moretti M, et al (2008) Resistance to rituximab therapy and local BAFF overexpression in Sjögren's syndrome-related myoepithelial sialadenitis and low-grade parotid B-cell lymphoma. *Open Rheumatol J*; 2:38-43.

Seror R, Sordet C, Guillevin L, et al (2007) Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. *Ann Rheum Dis*; 66:351-357.

Seror R, Ravaud P, Bowman S, et al (2011) EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Erratum in: *Ann Rheum Dis*; 70:880.

Shiboski SC, Shiboski CH, et al (2012) American College of Rheumatology classification criteria for Sjögren's syndrome: A data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance Cohort. *Arthritis Care Res*; 64:475-487

Tesfa D, Palmblad J (2011) Late-onset neutropenia following rituximab therapy: incidence, clinical features and possible mechanisms. *Expert Rev Hematol*; 4:619-625.

Varin MM, Le Pottier L, Youinou P, et al (2010) B-cell tolerance breakdown in Sjögren's syndrome: Focus on BAFF. *Autoimmunity Rev*; 9:604-608.

Vitali C, Bombardieri S, Jonsson R, et al (2002) Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*; 61:554-558.

Wolach O, Shpilberg O, Lahav M (2012) Neutropenia after rituximab treatment: new insights on a late complication. *Curr Opin Hematol*; 19:32-38.

Whitcher JP, Shiboski CH, Shiboski SC, et al (2010) A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's syndrome international registry. *Am J Ophthalmol*; 149:405-415.

Youinou P, Pers JO (2012) Latest update on the primary Sjögren's syndrome. *Presse Med*; 41 (9 pt 2):e437-439.

Corporate Confidential Information

15 Appendix 3: ESSDAI

Table 15-1 The EULAR Sjögren's syndrome disease activity index (ESSDAI): domain and item definitions and weights

Domain [weight]	Activity level	Description
Constitutional [3] Exclusion of fever of infectious origin and voluntary weight loss	No = 0 Low = 1 Moderate = 2	Absence of the following symptoms Mild or intermittent fever (37.5–38.5°C)/night sweats and/or involuntary weight loss of 5-10% of body weight Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy [4] Exclusion of infection	No = 0 Low = 1 Moderate = 2 High = 3	Absence of the following features Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging) Current malignant B-cell proliferative disorder
Glandular [2] Exclusion of stone or infection	No = 0 Low = 1 Moderate = 2	Absence of glandular swelling Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular or lachrymal swelling Major glandular swelling with enlarged parotid (>3 cm), or important submandibular or lachrymal swelling
Articular [2] Exclusion of osteoarthritis	No = 0 Low = 1 Moderate = 2 High = 3	Absence of currently active articular involvement Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min) 1–5 (of 28 total count) synovitis ≥6 (of 28 total count) synovitis
Cutaneous [3] Rate as 'no activity' stable long-lasting features related to damage	No = 0 Low = 1 Moderate = 2 High = 3	Absence of currently active cutaneous involvement Erythema multiforma Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis

Domain [weight]	Activity level	Description
Pulmonary* [5] Rate as 'no activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)	No = 0	Absence of currently active pulmonary involvement
	Low = 1	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with no breathlessness and normal lung function test
	Moderate = 2	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NYHA II) or abnormal lung function tests restricted to 70%>DL _{CO} ≥40% or 80%>FVC≥60%
	High = 3	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NYHA III, IV) or with abnormal lung function tests DL _{CO} <40% or FVC<60%
Renal [5] Rate as 'no activity' stable long-lasting features related to damage and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first	No = 0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 1	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 ml/min)
	Moderate = 2	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day or haematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinaemia-related renal involvement
Muscular* [6] Exclusion of weakness due to corticosteroids	No = 0	Absence of currently active muscular involvement
	Low = 1	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N<CK≤2N)
	Moderate = 2	Moderately active myositis confirmed by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N)
	High = 3	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)

Domain [weight]	Activity level	Description
PNS* [5] Rate as 'no activity' stable long-lasting features related to damage or PNS involvement not related to the disease	No = 0	Absence of currently active PNS involvement
	Low = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
	Moderate = 2	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensorimotor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High = 3	Highly active PNS involvement shown by NCS, such as axonal sensorimotor neuropathy with motor deficit $\leq 3/5$, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit $\leq 3/5$ or severe ataxia
CNS* [5] Rate as 'no activity' stable long-lasting features related to damage or CNS involvement not related to the disease	No = 0	Absence of currently active CNS involvement
	High = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit
Haematological [2] For anaemia, neutropenia, and thrombopenia, only autoimmune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia	No = 0	Absence of auto-immune cytopenia
	Low = 1	Cytopenia of auto-immune origin with neutropenia ($1000 < \text{neutrophils} < 1500/\text{mm}^3$), and/or anaemia ($10 < \text{haemoglobin} < 12 \text{ g/dl}$), and/or thrombocytopenia ($100000 < \text{platelets} < 150000/\text{mm}^3$) Or lymphopenia ($500 < \text{lymphocytes} < 1000/\text{mm}^3$)
	Moderate = 2	Cytopenia of auto-immune origin with neutropenia ($500 \leq \text{neutrophils} \leq 1000/\text{mm}^3$), and/or anaemia ($8 \leq \text{haemoglobin} \leq 10 \text{ g/dl}$), and/or thrombocytopenia ($50000 \leq \text{platelets} \leq 100000/\text{mm}^3$) Or lymphopenia ($\leq 500/\text{mm}^3$)
	High = 3	Cytopenia of auto-immune origin with neutropenia ($\text{neutrophils} < 500/\text{mm}^3$), and/or or anaemia ($\text{haemoglobin} < 8 \text{ g/dl}$) and/or thrombocytopenia ($\text{platelets} < 50000/\text{mm}^3$)

Domain [weight]	Activity level	Description
Biological [1]	No = 0	Absence of any of the following biological features
	Low = 1	Clonal component and/or hypocomplementaemia (low C4 or C3 or CH50) and/or hypergammaglobulinaemia or high IgG level between 16 and 20 g/l
	Moderate = 2	Presence of cryoglobulinaemia and/or hypergammaglobulinaemia or high IgG level >20 g/l, and/or recent onset hypogammaglobulinaemia or recent decrease of IgG level (<5 g/l)

CIDP, chronic inflammatory demyelinating polyneuropathy; CK, creatine kinase; CNS, central nervous system; DL_{CO}, diffusing CO capacity; EMG, electromyogram; EULAR, European League Against Rheumatism; FVC, forced vital capacity; GFR, glomerular filtration rate; Hb, haemoglobin; HRCT, high-resolution computed tomography; IgG, immunoglobulin G; NCS, nerve conduction studies; NYHA, New York Heart Association classification; Plt, platelet; PNS, peripheral nervous system.

*Clinical investigator subjective scoring based on availability of concurrent clinical data.

16 Appendix 4: ESSPRI

Your physician has asked you to answer several questions relating to your disease. To answer to these questions, please take into account how bad your symptoms have been at their worst during the last **two weeks** only.

Please **tick one box only** that best reflects your response.

Please take care to answer **all the questions**.

Example:

No pain	<table border="1"><tr><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input checked="" type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td></tr><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	6	7	8	9	10	Maximal imaginable pain
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>														
0	1	2	3	4	5	6	7	8	9	10														

EVALUATION SCALES

1. How severe has your **dryness** been during the last 2 weeks?

No dryness	<table border="1"><tr><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td></tr><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	6	7	8	9	10	Maximal imaginable dryness
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>														
0	1	2	3	4	5	6	7	8	9	10														

2. How severe has your **fatigue** been during the last 2 weeks?

No fatigue	<table border="1"><tr><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td></tr><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	6	7	8	9	10	Maximal imaginable fatigue
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>														
0	1	2	3	4	5	6	7	8	9	10														

3. How severe has your **pain** (joint or muscular pains in your arms or legs) been during the last 2 weeks?

No pain	<table border="1"><tr><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td></tr><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	6	7	8	9	10	Maximal imaginable pain
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>														
0	1	2	3	4	5	6	7	8	9	10														

4. How severe has your **mental fatigue** (not thinking clearly, finding it hard to concentrate, forgetting things, or making mistakes) been during the last 2 weeks?

No pain	<table border="1"><tr><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td></tr><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr></table>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	0	1	2	3	4	5	6	7	8	9	10	Maximal imaginable mental fatigue
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>														
0	1	2	3	4	5	6	7	8	9	10														

5. How severe has your **ocular** (eye) **dryness** been during the last 2 weeks?

No dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable dryness
	0	1	2	3	4	5	6	7	8	9	10

6. How severe has your **oral** (mouth) **dryness** been during the last 2 weeks?

No dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable dryness
	0	1	2	3	4	5	6	7	8	9	10

7. How severe has your **skin dryness** been during the last 2 weeks?

No dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable dryness
	0	1	2	3	4	5	6	7	8	9	10

8. How severe has your **nasal dryness** been during the last 2 weeks?

No dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable dryness
	0	1	2	3	4	5	6	7	8	9	10

9. How severe has your **tracheal** (breathing tubes) **dryness** been during the last 2 weeks?

No dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable dryness
	0	1	2	3	4	5	6	7	8	9	10

10. How severe has your **vaginal dryness** been during the last 2 weeks?

No dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Maximal imaginable dryness
	0	1	2	3	4	5	6	7	8	9	10

If not relevant tick this box ☐

Preliminary Explanation:

You have just evaluated the severity of your symptoms. However, in your everyday life some may be more important to you than others. You are now going to evaluate their importance, try to reflect this distinction in your answers.

11. Among the following symptoms, please identify the one you consider the **most** in need for improvement (**tick only one box**)

Dryness ☐

Fatigue ☐

Pain ☐

Mental Fatigue ☐

12. Among the following symptoms, please rank them by priority order: - from **1**: the **most** in need of improvement → to **4**: the **least** in need of improvement.

Dryness

Fatigue

Pain

Mental Fatigue

/___/

/___/

/___/

/___/

13. Among the following dryness symptoms, please identify the one you consider the **most** in need for improvement (**tick only one box**)

Ocular ☐

Oral ☐

Skin ☐

Nasal ☐

Tracheal ☐

Vaginal ☐

14. Among the following dryness symptoms, please rank them by priority order: - from **1**: the **most** in need of improvement → to **6**: the **least** in need of improvement.

Ocular

Oral

Skin

Nasal

Tracheal

Vaginal

/___/

/___/

/___/

/___/

/___/

/___/

15. How important is it to you to get rid of your dryness?

Not important at all

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10

Extremely
important

16. How important is it to you to get rid of your fatigue?

Not important at all

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10

Extremely
important

17. How important is it to you to get rid of your pain?

Not important at all	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Extremely important
	0	1	2	3	4	5	6	7	8	9	

18. How important is it to you to get rid of your mental fatigue?

Not important at all	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Extremely important
	0	1	2	3	4	5	6	7	8	9	

19. Considering now your symptoms related to your Sjögren's syndrome (e.g., dryness, your fatigue, pain and your mental fatigue), as well as their consequences on your professional or personal life, how severe was your Sjogren's syndrome during the last 2 weeks?

Inactive disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Very active disease
	0	1	2	3	4	5	6	7	8	9	

20. How long has it taken you to complete this questionnaire?

_____ minutes

21. How easy or difficult have you found it to complete this questionnaire?

Very easy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Very difficult
	0	1	2	3	4	5	6	7	8	9	

Comments

17 Appendix 5: SF-36

Will be provided separately.

18 Appendix 6: MFI

Will be provided separately.

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information